

**MINISTRY OF HEALTH**

**GUIDELINES FOR DIAGNOSIS AND  
TREATMENT OF HIV/AIDS**

**HANOI, 2005**

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## LIST OF ABBREVIATIONS

3TC	Lamivudine	HPV	Human papiloma virus
ABC	Abacavir	HSV	Herpes simplex virus
AIDS	Acquired immunodeficiency syndrome	IDU	Injecting drug user
AFB	Acid fast bacilli	IgG	Immunoglobulin G
ALT (SGPT)	Alanin aminotransferase	IgM	Immunoglobulin M
ANC	Ante-Natal Care	IM	Intramuscularly
anti-HBc	Anti-Hepatitis B core antigen	IV	Intravenously
anti- HBe	Anti-Hepatitis B envelop antigen	LDH	Lactate dehydrogenase
anti- HCV	Anti-Hepatitis C antibody	LIP	Lymphoid interstitial pneumonia
ARV	Antiretroviral	LPV	Lopinavir
AST (SGOT)	Aspartat aminotransferase	MAC	Mycobacterium avium complex
AZT	Zidovudine	NFV	Nelfinavir
BCG	Bacillus Calmett-Guerrin	NRTI	Nucleoside reverse transcriptase inhibitor
b.i.d	Two times a day	NNRTI	Non-nucleoside reverse transcriptase inhibitor
BAL	Broncho-alveolar lavage	NVP	Nevirapine
CBC	Complete blood count	OI	Opportunistic infections
CDC	Centers for Disease Control and Prevention	PCP	<i>P.jiroveci</i> pneumonia
CMV	Cytomegalovirus	PCR	Polymerase chain reaction
CNS	Central nervous system	PI	Protease inhibitor
CRP	C-reactive protein	PMTCT	Prevention of Mother-to-Child Transmission
CSF	Cerebrospinal fluid	PO	Per-orally
CT	Computerized tomography	QD	Once daily
d4T	Stavudine	RNA	Ribonucleic acid
ddI	Didanosine	RPR	Rapid plasma reagin
DNA	Desoxyribonucleic acid	RTV	Ritonavir
DOT	Directly observed therapy	TB	Tuberculosis
EFV	Efavirenz	TCD4	CD4 bearing T lymphocytes
ELISA	Enzyme-linked immunosorbent assay	TDF	Tenofovir
HAART	Highly active antiretroviral therapy	TMP-SMX	Trimethoprim-sulfamethoxazol
HBeAg	Hepatitis B Envelop Antigen	TLC	Total Lymphocyte Count
HBsAg	Hepatitis B surface antigen	t.i.d	Three times a day
HBV	Hepatitis B virus	t.i.w	Three times in a week
HCV	Hepatitis C virus	TPHA	T.pallidum hem-agglutination
HIV	Human immunodeficiency virus	VDRL	Venereal disease research laboratories
		VZV	Varicella Zoster Virus
		WHO	World Health Organization

## **I. THE DIAGNOSIS AND STAGING SYSTEMS OF HIV INFECTION**

### **1. The diagnosis and staging system of HIV Infection in Adults**

**1.1. The diagnosis:** The serum sample of a person is considered HIV-positive when it is reactive to 3 HIV serological tests with different methods of antigen preparation or different methods of testing (strategy III).

Only authorized by MoH laboratories can give the positive HIV results.

### **1.2. The staging system:**

- **Clinical staging:** HIV infection is divided into four stages, based on HIV-related conditions, e.g. weight loss, OIs, malignancies, and status of physical activity (see Annex 1 - HIV/AIDS Clinical Staging in Adults and Adolescents). HIV-infected people with diseases of clinical stage IV are confirmed AIDS.
- **Laboratory staging:** HIV-infected adults with TCD4  $\leq$  200 cells/mm<sup>3</sup> are considered severely immuno-suppressed. In the settings where TCD4 testing is not available, total lymphocyte count (TLC) can be used instead. HIV-infected people with TLC  $\leq$ 1200 cells/mm<sup>3</sup> and HIV-related symptoms are considered severely immuno-suppressed.

### **2. The diagnosis and staging system of HIV Infection in Children**

#### **2.1. The diagnosis**

- Infants < 18 months: positive virological tests (e.g. p24, PCR DNA or RNA), if available
- Children  $\geq$  18 months: 3 positive HIV antibody tests as in adults. Breast fed children should be tested after breast feeding discontinued for 6 weeks.

#### **2.2. The staging systems:**

- **Clinical staging:** HIV infection is divided into four stages. HIV-infected children with clinical stage IV are considered AIDS. In case no virological testing available, children under 18 months born to HIV-positive mothers are diagnosed with AIDS if they are HIV seropositive and have AIDS defining diseases. (See Annex 2 – Pediatric Clinical Staging of HIV/AIDS)
- **Laboratory staging:** The immunostatus of HIV-infected children is assessed by the age-specific TCD4 cell count and percentage of TCD4/TLC (see Annex 3: Immunologic categories for HIV-infected children Based on age-specific TCD4 lymphocyte counts and percentage of total lymphocytes). Children with TCD4  $\leq$ 15% are considered AIDS.

## **II. CLINICAL MANAGEMENT OF PERSONS WITH HIV/AIDS**

### **1. Initial Assessment**

#### **1.1. History taking:**

- Risk behaviours
- History of STDs
- History of prior OIs and HIV-related illnesses, including TB
- History of other diseases
- History of medicines used (OI prophylaxis and treatment, ARV..)
- History of allergy
- Signs and symptoms of current illness

#### **1.2. Physical exams:**

- Do complete physical exam, including weight, look for peripheral lymphadenopathy, abnormalities from organs and systems
- Assess the clinical stage of HIV disease
- Look for OIs and HIV-related illnesses
- Screen for TB
- Assess possibility of pregnancy

### 1.3. Laboratory testing:

- Complete Blood Count (CBC): do hemoglobin/hematocrit, total lymphocyte count (TLC). If not available, TLC can be estimated by the following:

$$\text{TLC} = \text{White Blood Count} \times \% \text{ lymphocytes}$$

- TCD4 cell count, if possible
- Chest X-ray
- Sputum microscopy for AFB
- Liver enzyme ALT, if hepatitis is suspected
- HBsAg if possible, and anti-HCV if the patient has history of IDU
- PAP smear for women
- Pregnancy test if indicated
- Other laboratory tests for detecting OIs if indicated

## 2. Counselling and Support

- Give post-test counselling
- Explain about the course of the disease and the plan for care and treatment, the needs for follow-up visits
- Counsel on active living, nutrition and healthy living (see Annex 4: Advice on Healthy Living for Persons with HIV/AIDS)
- Counsel on prevention of HIV transmission: safe sex, harm reduction measures
- Counsel on the use of birth control methods, prevention of mother to child transmission of HIV if the woman decides to have babies
- Counsel on adherence to OI prophylaxis and ART if indicated

## 3. Vaccination

**TABLE 1: Recommendations for vaccination in HIV-infected children**

Vaccine	HIV-exposed infants, before diagnosis is known	HIV-infected children, clinical stages I, II, III	HIV-infected children, clinical stage IV
<i>Nationally-supported vaccines</i>			
BCG	As scheduled*	As scheduled	DO NOT GIVE
Diphtheria-Pertussis-Tetanus	As scheduled	As scheduled	As scheduled
Poliomyelitis oral	As scheduled	As scheduled	Give parenteral vaccine, if possible.
Hepatitis B	As scheduled	As scheduled	As scheduled

Measles	As scheduled	At 11-12 years#	DO NOT GIVE
Japanese encephalitis	As scheduled	As scheduled	As scheduled
<i>Optional vaccines</i>			
Haemophilus influenzae type B	At 2, 4, 6 months	At 12-15 months	
Varicella	At 12,15 months	At 11-12 years#	DO NOT GIVE
Influenza	From 6 months, once in every year		As scheduled
Mumps	At 12-15 months	At 11-12 years	DO NOT GIVE
Rubella	At 12-15 months	At 11-12 years	DO NOT GIVE

\* Do not give to infants with congenital defects, pre-term babies or babies with low birth weight. Vaccinated infants should be followed to detect and treat for complications of BCG.

# Give vaccination if the child has not been vaccinated

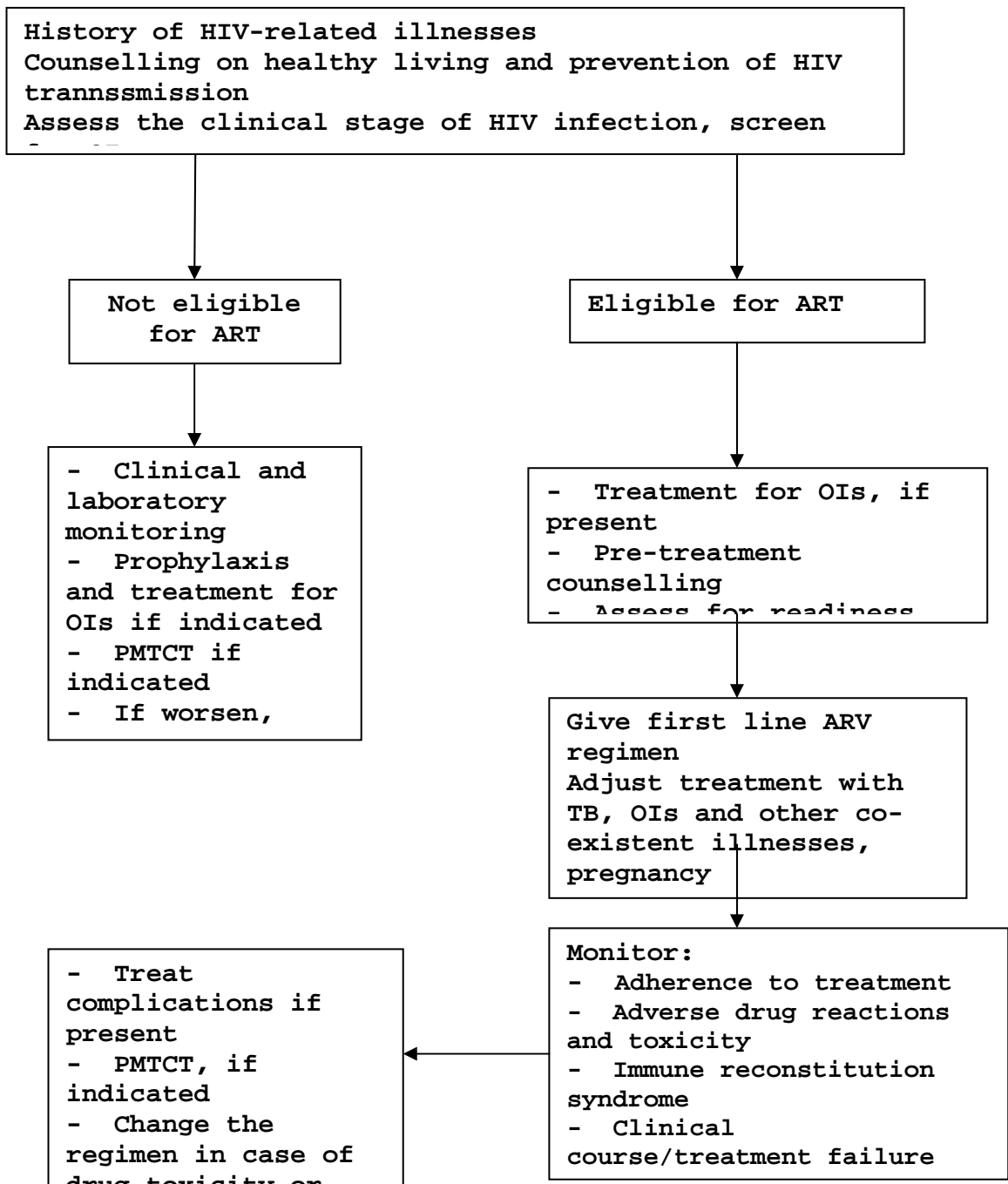
- HIV-infected persons not exposed to hepatitis B (no anti-HBc, HBsAg) should receive hepatitis B vaccine.

#### **4. Clinical Monitoring**

HIV-infected persons should have regular follow-up visits every 3-6 months if asymptomatic, and at any time if symptoms present.

- Do physical examination, define the clinical stage of HIV infection
- Do laboratory assessments:
  - + CBC every 6 months
  - + TCD4 count every 6 months, if available
  - + Chest X-ray and others if indicated
- Counsel and schedule for the next visit if the patient is asymptomatic
- Give OI prophylaxis if indicated
- Treat OIs and HIV related illnesses, if present. Hospitalize the patient or refer to higher level if severe
- Refer for consultation of specialists if TB or STDs are suspected
- Refer pregnant women to Obstetric-Gynecology services for PMTCT
- If the patient fullfills clinical and immunological criteria for ART: give pre-treatment counselling
  - + Patient is not ready for ART: continue counselling and schedule next follow-up visit
  - + Patient is ready for ART: give appropriate first line regimen

## CLINICAL MANAGEMENT OF HIV-INFECTED PATIENTS



### III. PREVENTION OF OPPORTUNISTIC INFECTIONS

#### 1. Prophylaxis for *P.jiroveci* pneumonia (PCP)

**Indications:**

- Patients in clinical stage III and IV, irrespective of the TCD4 count
- Patients in clinical stage I and II with the TCD4 count < 200 cells/mm<sup>3</sup>, or clinical stage II if the TLC ≤ 1,200/mm<sup>3</sup>

**Preferred regimen:** TMP-SMX 1 double-strength (DS) tablet, or 2 single-strength (SS) tablet per-orally (PO) q.d, or 2 DS tablet PO three times in a week (t.i.w)

**Alternative regimen:** Dapsone 100mg. PO q.d, or

**Duration:** lifelong. Can be discontinued when patients are on HAART with TCD4 count > 200 cells/mm<sup>3</sup> x > 3 months.

**Attention:** + Patients on treatment or prophylaxis for toxoplasma encephalitis do not need independent PCP prophylaxis.  
+ Do not give TMP-SMX prophylaxis to pregnant women in the first trimester of pregnancy.

#### PCP Prevention in HIV infected and HIV-exposed children:

**Indications:** - HIV-infected children in clinical stage II, III, or IV, or with TCD4 percentage of < 15%.  
- Prophylaxis is recommended for all children born to HIV-infected mothers, beginning from 4-6 weeks of age.

**Preferred regimen:** TMP-SMX 5mg/kg/day by TMP in syrup or tablets, once a day.

**Alternative regimen:** Dapsone 2 mg/kg q.d or 4 mg/kg PO, every week for children aged >1 year.

**Duration of prophylaxis:** Lifelong for children with confirmed HIV infection, who are not on ART

**Discontinuation of prophylaxis:** - When the HIV status of the child is ruled out  
- HIV-infected children are on ARV and have signs of immune recovery (TCD4 percentage > 15% for more than 3-6 months)

**Attention:** PCP prophylaxis with TMP-SMX can also prevent toxoplasma encephalitis in HIV infected children

#### 3. Prophylaxis for Toxoplasma Encephalitis

**Indications:** HIV-infected persons with positive antitoxoplasma IgG antibodies when the TCD4 count < 100 cells/mm<sup>3</sup>. (Toxoplasma serodiagnosis is currently not available in Vietnam)

**Regimen:** TMP-SMX 160-800 mg/day.

**Duration of prophylaxis:** lifelong. Primary prophylaxis can be discontinued if patients are on HAART with the TCD4 count > 200/mm<sup>3</sup> x ≥ 3 months.

**Attention:**

- PCP prophylaxis with TMP-SMX can also prevent toxoplasma encephalitis
- Do not give TMP-SMX prophylaxis to pregnant women in the first trimester of pregnancy; can discontinue the prophylaxis and monitor closely. Do not give pyrimethamine prophylaxis in the whole pregnancy.

### 3. Prophylaxis for Cryptococcal Meningitis

**Indications:** - HIV infected persons in stage IV, irrespective of TCD4 count  
- HIV infected persons with TCD4 count < 100 cells/mm<sup>3</sup>.

**Regimen:** fluconazole 200 mg PO every other day or 400 mg (or 150mg tablets x 3) once in a week

**Duration of prophylaxis:** lifelong. Can be discontinued if the patient is on HAART with the TCD4 count > 100 cells/mm<sup>3</sup> x 3-6 months.

**Attention:** Do not give fluconazole prophylaxis for pregnant women; can discontinue the prophylaxis and monitor closely.

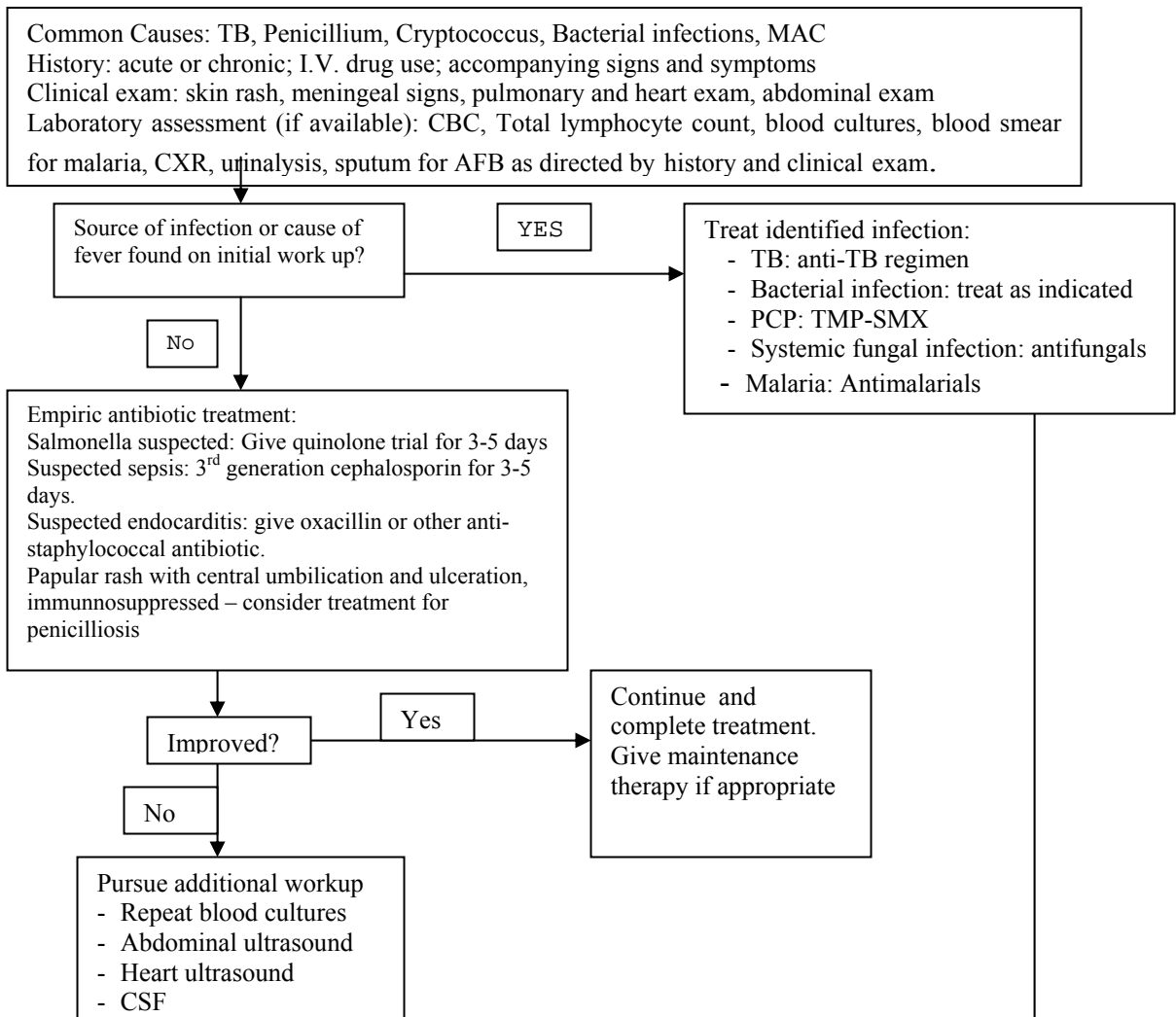
**Table 2: Recommendations for specific prevention of OIs in HIV/AIDS persons based on TCD4 cell count**

<b>Immune stage</b>	<b>Specific prevention</b>
- Clinical stage III, IV; - TCD4 <200 cells/mm <sup>3</sup> or clinical stage II and the total lymphocyte count < 1,200 cells /mm <sup>3</sup>	- PCP* prophylaxis
- Clinical stage IV or TCD4 < 100 cells/mm <sup>3</sup>	- Prophylaxis of Toxoplasma encephalitis - Prophylaxis for Cryptococcosis

\* PCP prophylaxis with TMP-SMX is also effective in preventing toxoplasma encephalitis.

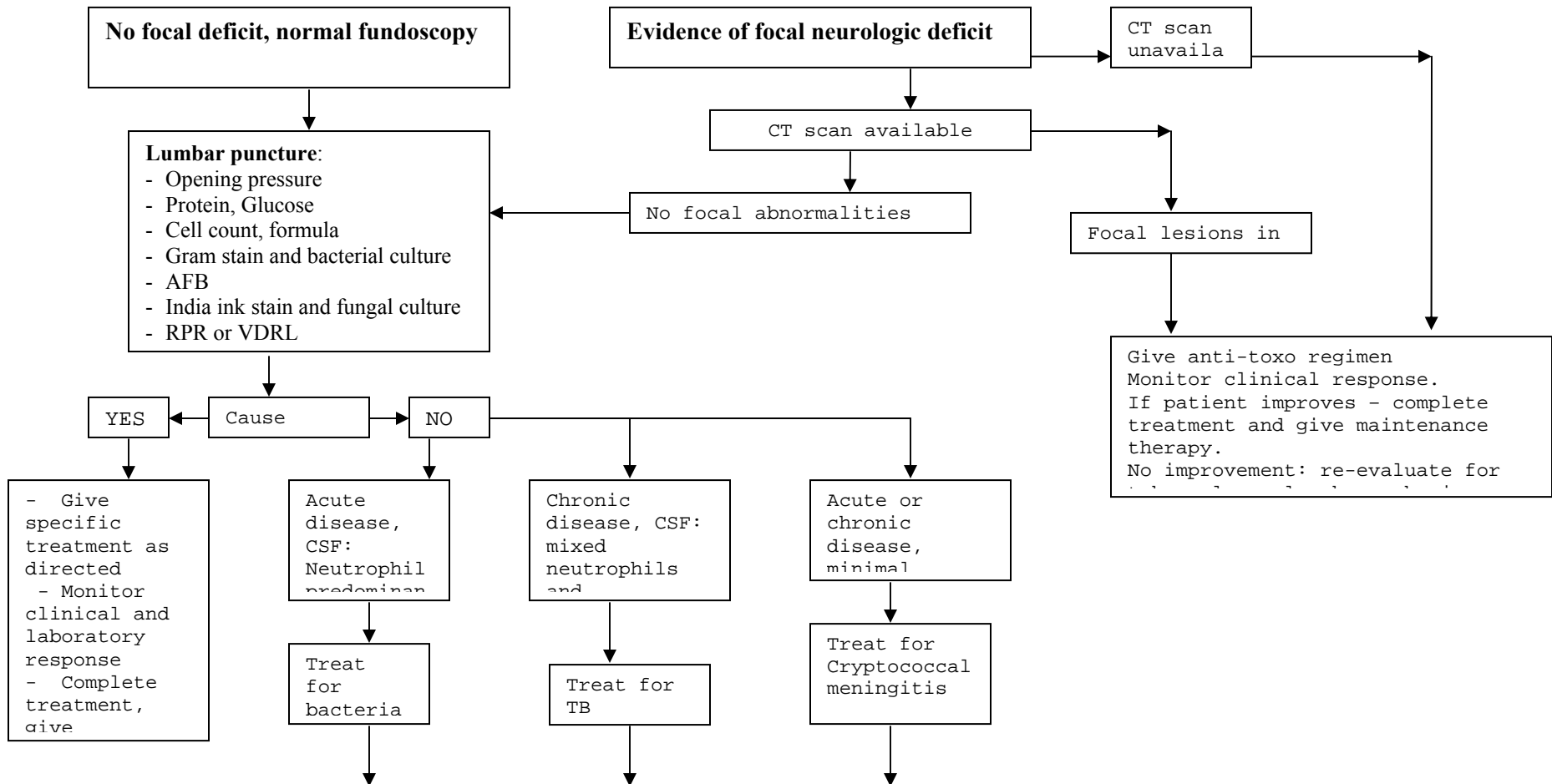
## IV. APPROACH TO COMMON CLINICAL SYNDROMES IN HIV/AIDS PATIENTS

## 1. Prolonged Fever



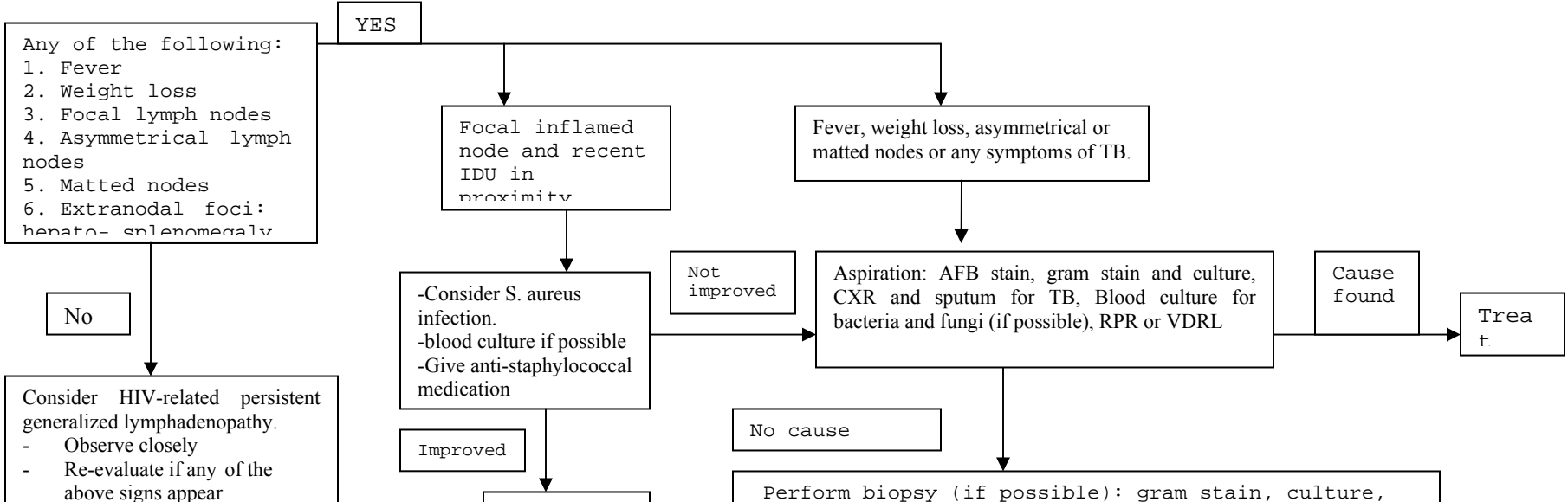
## 2. Headache and Neurologic Changes

Common Causes: Cryptococcal Meningitis, Bacterial meningitis, Toxoplasmosis, TB meningitis  
 History: Acute or chronic course, fever, History of TB  
 Clinical exam: Meningeal signs, focal neurologic deficits, accompanying signs, fundoscopy if patient is obtunded or if unable to rule out focal deficits  
 Laboratory assessment: WBC, serum glucose, blood culture, chest X-ray.



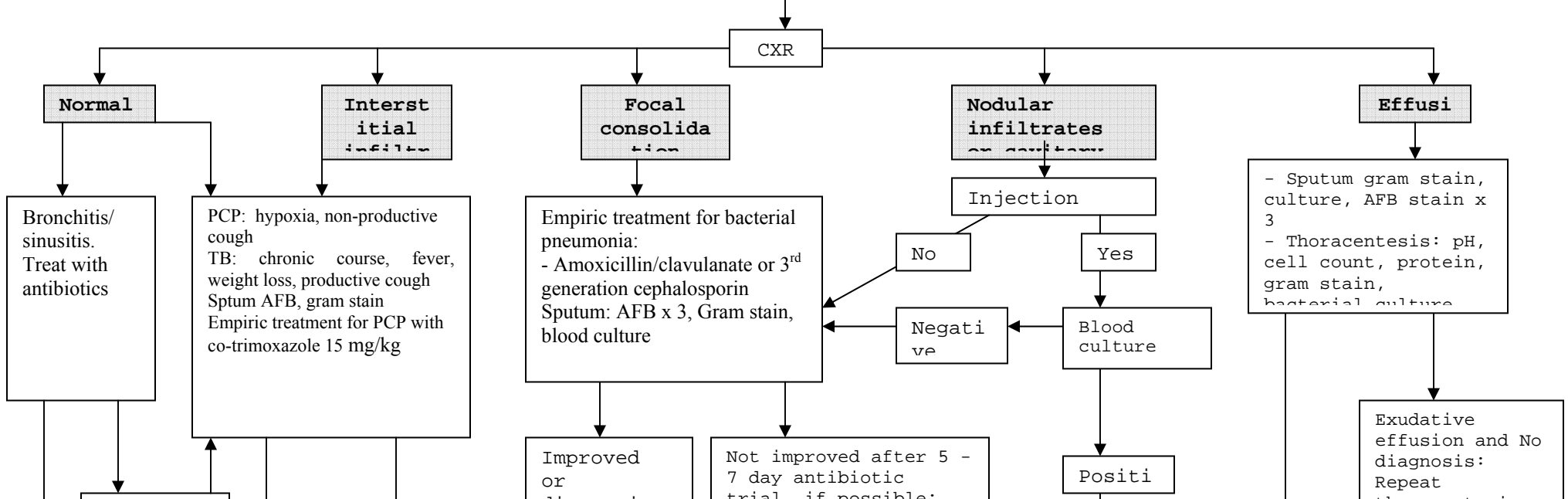
**Monitor clinical response and repeat lumbar puncture**  
 - Patient improves: continue and complete treatment; give maintenance therapy if needed  
 - Patient does not improve: re-evaluate. Consider TB

Common causes: TB, *S.aureus* infection, fungal infection, syphilis, MAC, malignancy, HIV-related persistent generalized lymphadenopathy  
 History: Duration of lymphadenopathy; fever, weight loss. History of TB or syphilis, IDU  
 Clinical exam: Focal or diffuse lymphadenopathy, skin rash, lung exam, hepatosplenomegaly



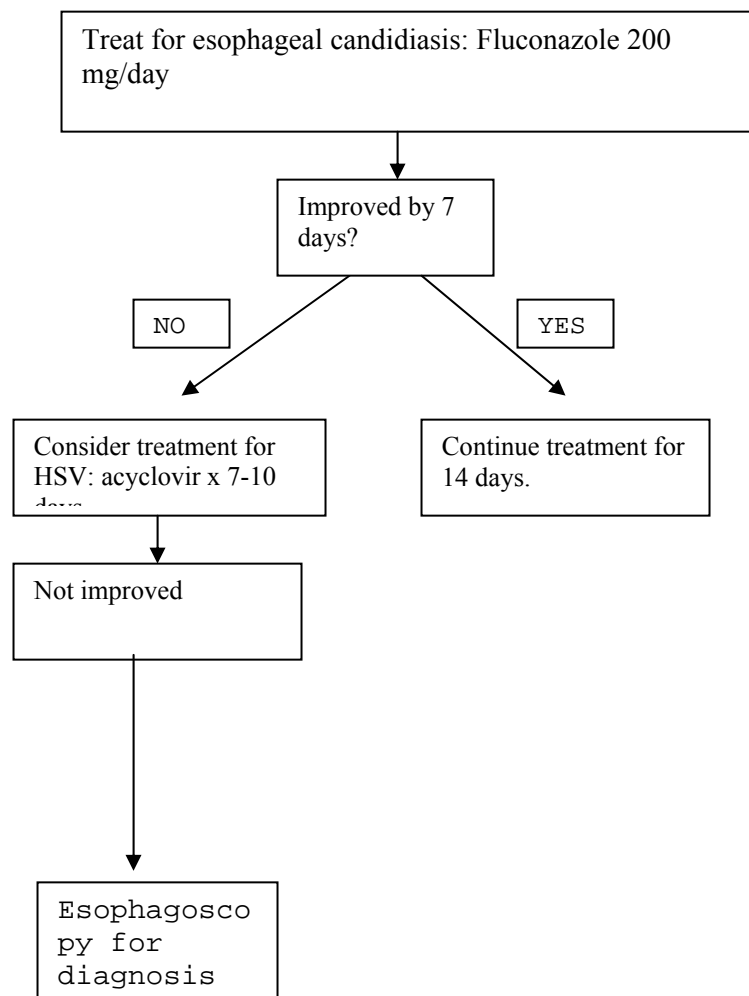
#### 4. Respiratory symptoms

Common causes: Bacteria, TB, PCP  
 History: acute or chronic shortness of breath, fever, cough, sputum, history of IDU  
 Physical exam: vital signs, cyanosis, effusion, rales, consolidation, clubbing, skin lesions



## 5. Odynophagia

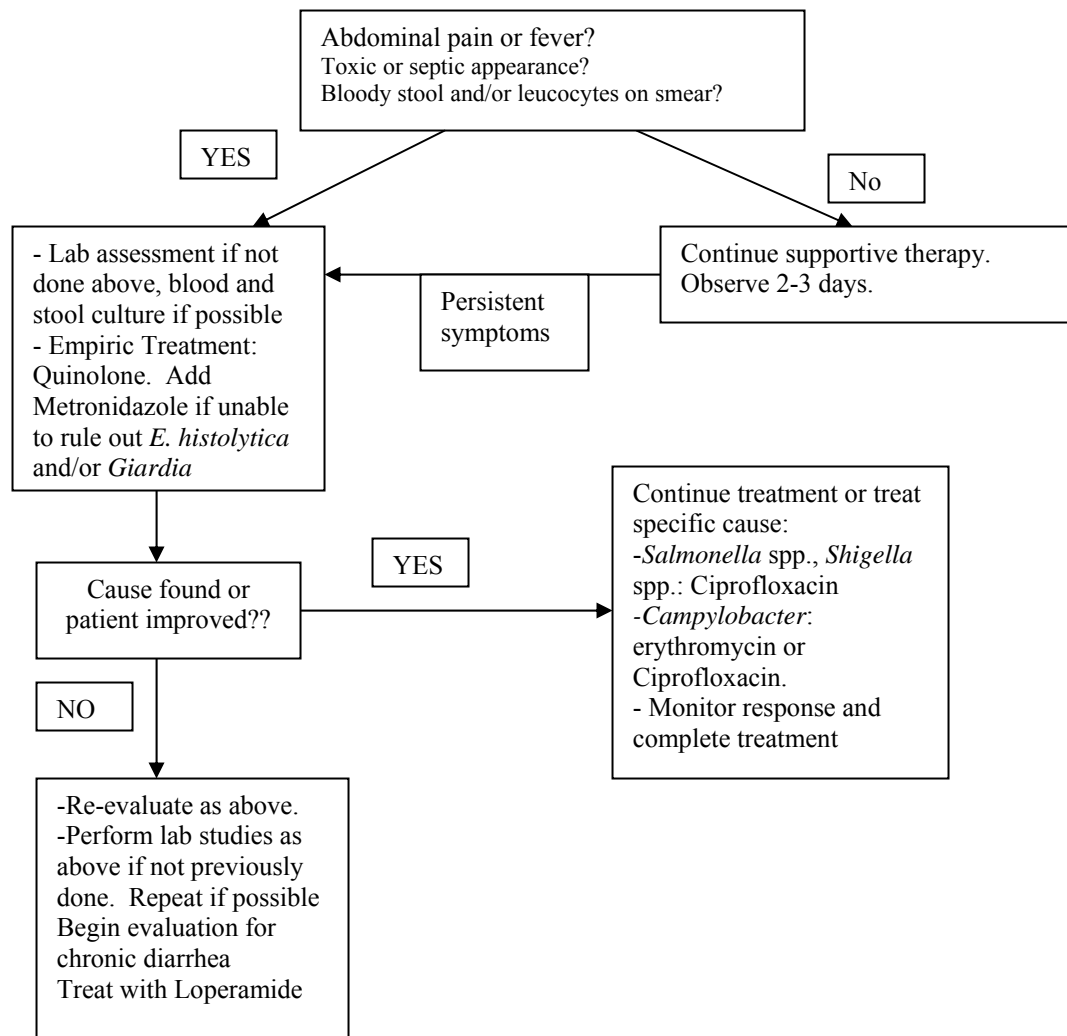
Common Causes: Candida, HSV, CMV, HIV  
History: Pain or difficulty with swallowing, decreased oral intake.  
Review of History: Note any new medications, any signs of AIDS  
Clinical exam: Note any oral thrush or ulcers, dehydration,



## 6. Diarrhea

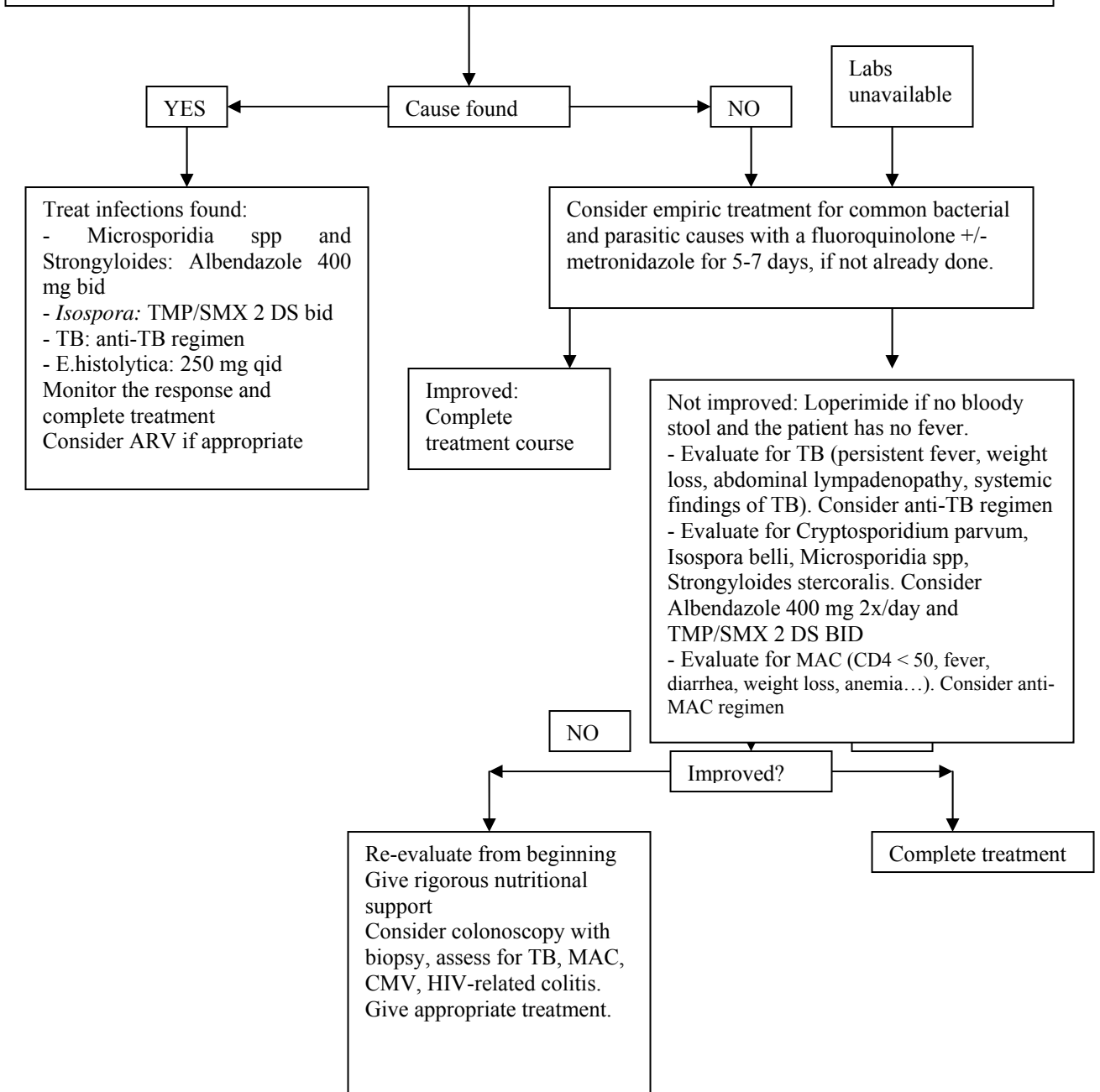
### a. Acute Diarrhea (Presence of >3 loose stools/day < 14 days)

Common causes: *Salmonella*, *Campylobacter*, *Shigella*, *E. coli*, *Clostridium difficile*, *Giardia*, *Entamoeba histolytica*, medication side effect  
 History: Duration and severity of diarrhea, abdominal pain, presence of blood and mucous in stool, fever, weight loss, drugs administered before and after onset of diarrhea  
 Clinical exam: Fever, dehydration, nutritional status, other concurrent OIs, signs of abdominal perforation  
 Laboratory assessment CBC, stool evaluation for fecal leukocytes and erythrocytes, culture, ova and parasites (if possible)  
 Initial support: Give rehydration (oral and IV), nutritional support.



**b. Chronic Diarrhea** (Presence >3 loose stools/day  $\geq$  14 days)

Common causes: TB, Salmonella, Cryptosporidia, Microsporidia, Isospora, Cyclospora, MAC, HIV  
 History: Fever, abdominal pain, flatulence, anorexia, weight loss, character of stool.  
 Clinical exam: Dehydration, weight, nutritional status, immune status, other systemic signs.  
 Laboratory assessment: CBC with total lymphocyte count, stool evaluation for fecal leukocytes, ova and parasites, stool AFB, blood culture if fever, evaluation for TB  
 Initial support: Oral and IV hydration as needed, correct electrolyte imbalance, nutritional support



## 7. Skin lesions

History: duration of illness, evolution of the lesions, accompanying fever; history of allergy, drug exposure (especially cotrimoxazole, penicillins, cephalosporins, nevirapine, efavirenz), history of syphilis.  
 Clinical exams: characteristics of lesions, distribution, accompanying itching; systemic symptoms  
 Consider early referral for scraping or biopsy if diagnosis is in question

Skin nodules

Penicilliosis (nodules with central necrotic umbilication)  
 Molluscum contagiosum cryptococcosis or TB.  
 Condyloma acuminata: Verrucous lesions

Suspected penicilliosis: Do skin scraping, with microscopy and culture.  
 Give appropriate treatment  
 Monitor response

Vesicular

- Vesicles within a dermatome; burning or pain: consider zoster  
 - Discrete vesicles: consider herpes simplex

Give acyclovir for HSV and VZV disease for 7-10 days if the patient is in early stage; if in late stage – give antibacterials and topical antiseptics

Macular or papular rash

Differential dx:  
 - Drug reaction  
 - Syphilis  
 - Scabies: papules, severe itch, burroughs may be seen.

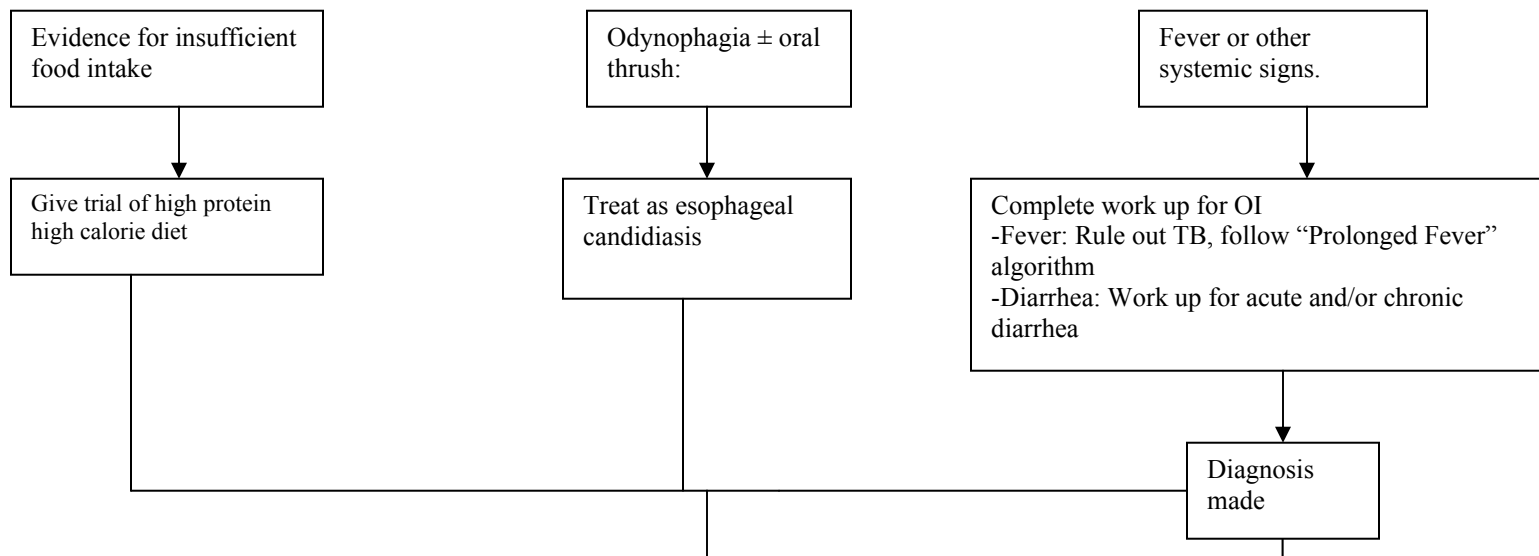
**-Suspected Drug reaction:** If reaction is due to ARV, refer to higher level for management  
**-If syphilis is suspected:** Do RPR, VDRL. Consider LP to rule out CNS disease

Rashes or conditions associated with HIV

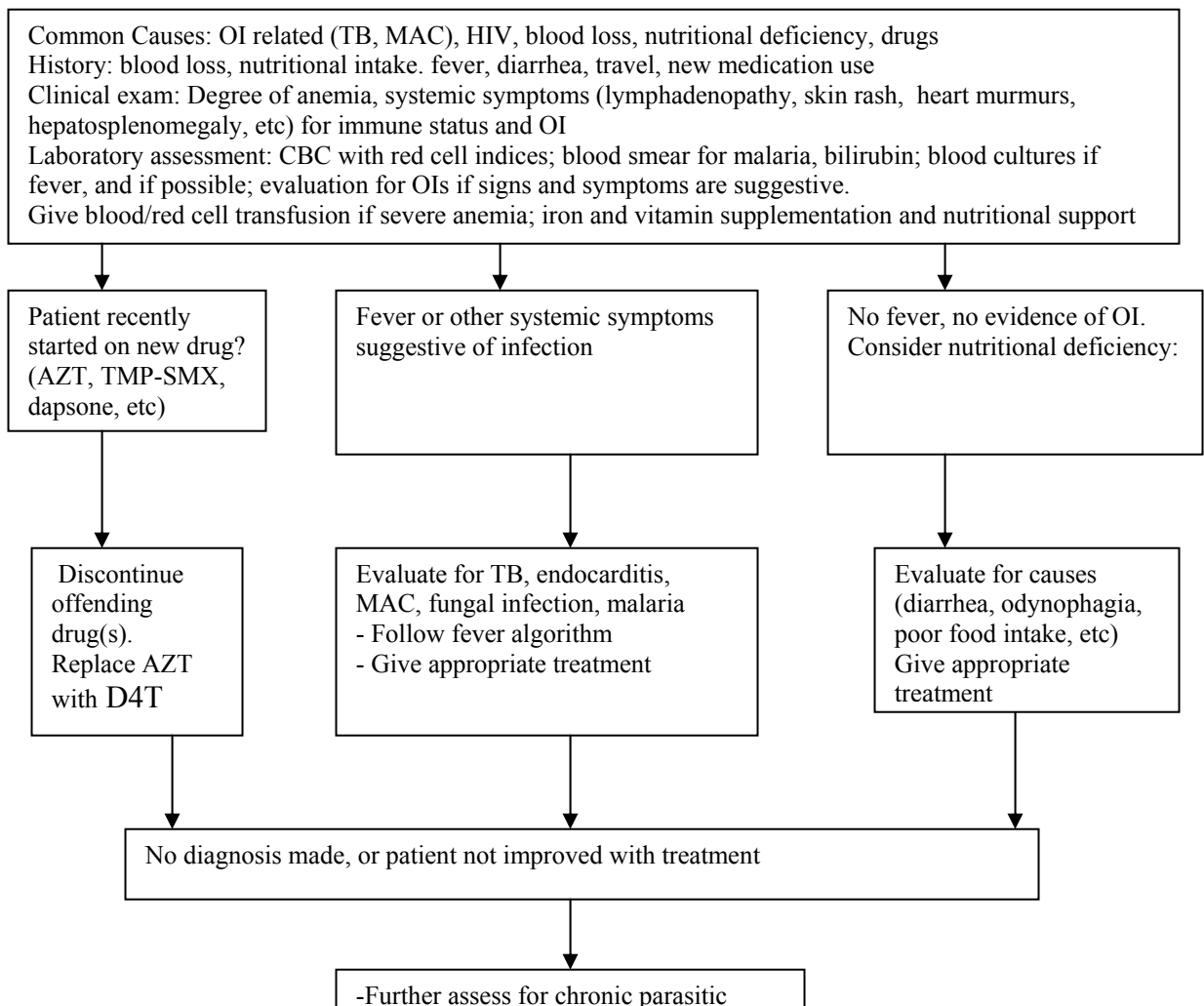
Scaly rash along nasolabial fold, hairline: Seborrheic dermatitis.  
 - Eosinophilic folliculitis: Acneiform lesions along face, chest, back  
 - Papular pruritic eruptions: large pruritic eruptions seen in advanced immunosuppression  
 - HIV related dry skin and itch.  
 Psoriasis: Pruritic rash with silver scale.

## 8. Wasting (Lost of >10% of body weight)

Common Causes: OIs, such as TB, Chronic diarrheas caused by enteric parasites, fungal infection and MAC, candida esophagitis, insufficient caloric intake, HIV  
History: Duration and degree of weight loss, fever, cough, diarrhea, caloric intake.  
Clinical exam: Dehydration, systemic signs and symptoms.  
Initial support: counsel on nutritional foods. increased caloric intake. vitamin and mineral supplementation

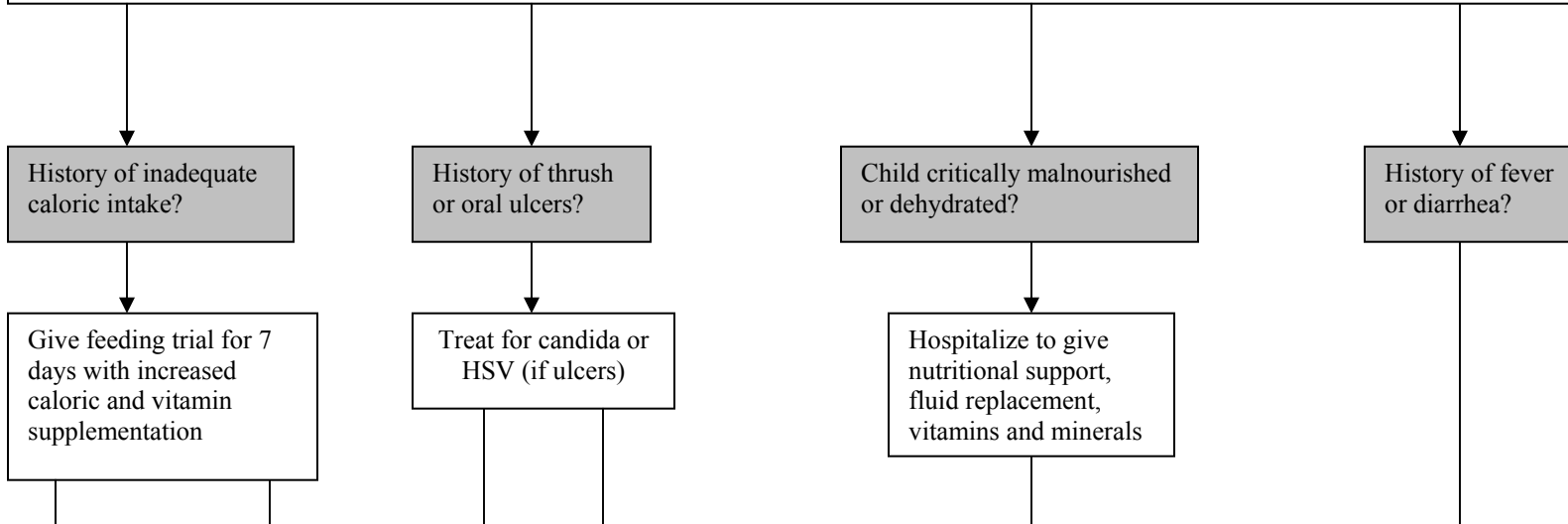


## 9. Anemia (Hemoglobin <12g/L in men and <10g/L in women)



## 10. Failure to Thrive in Pediatric Patients

**Definitiaion:** *Moderate* failure to thrive: weight = 60-80% of normal for age/height; *severe* failure to thrive: weight = <60% of normal for age/height, or weight 60-80% of normal for height if edema present  
**Common causes:** recurrent or occult infections; oral or esophageal candidiasis, inability to provide adequate amounts of food/calories; malabsorption and diarrhea, vomiting, chronic HIV infection  
**History:** Severity of weight loss, signs of occult infection, history of diarrhea or vomiting, feeding practice.  
**Clinical Exam:** Weight and height, complete exam looking for signs of occult infection  
**Initial support:** Hydration and nutritional support. Begin evaluation for ARV if child meets WHO criteria.



## **D. THE DIAGNOSIS, TREATMENT AND PREVENTION OF COMMON OPPORTUNISTIC INFECTIONS IN ADULTS WITH HIV/AIDS**

Opportunistic infections are the major cause of morbidity and mortality in persons with HIV/AIDS. The frequency and clinical manifestations of OIs depend on the degree of immunodeficiency of the patients, risky behaviours and other factors. The diagnosis of OIs should be based on the clinical manifestations of the disease, supportive microbiologic analyses, imaging studies, available epidemiological data and understanding of the patient's immunodeficiency such as TCD4 cell count, or the total lymphocyte count (see Annex 5: Common infections in HIV based on TCD4 count). HIV-infected patients with OIs need requiring timely diagnosis and appropriate treatment to minimize the morbidity and mortality. Certain OIs require lifelong suppressive therapies to reduce the recurrence .

### **I- FUNGAL INFECTIONS**

#### **1.1. Candidiasis:**

##### ***Clinical manifestations***

Candidiasis often occurs in immunodeficient stage (TCD4 < 200 cells/mm<sup>3</sup>), can be severe, persistent and frequently relapse

- Oropharyngeal and esophageal Candidiasis : creamy white, easily removable plaques or spots on the tongue, gums, buccal mucosa, palate. If the lesions spread to the throat and esophagus, the patient usually complains of swallowing difficulty and/or pain on swallowing.
- Skin Candidiasis : Lesions are red macules with crusts, surrounded by red papules, can come along with pustules or furuncles, which are difficult to treat. Usually seen in skin folds in armpits, inguina, around and in the nails, etc.
- Vulvovaginal Candidiasis : The patient experiences itching and burning; vaginal discharge is creamy white cheese-like plaques. Vulvo-vaginal area is erythematous, swollen and painful. Relapses are common.

##### **Diagnosis**

- Based primarily on the appearance of the lesions
- Esophageal endoscopy is indicated in case the symptoms do not respond to antifungal drugs
- Wet mount preparation for the yeast when the patient does not respond to treatment
- Culture and identification of the yeast if the appearance of lesions is not typical

##### **Treatment**

###### ***Initial treatment***

- Oral Candidiasis

Topical medications : Clotrimazole troche, Daktarin oral gel (miconazole), Nystatin oral suspension.

Oral medications: Fluconazole 100-200 mg/d (or 150mg tab x 1-2 times/day), or Itraconazole 200 mg/d, or Ketoconazole 200mg bid for 7-14 days.

(Ketoconazole is less effective compared to Itraconazole and less frequently used due to hepatotoxicity ; concurrent use with rifampin is not recommended.)

- Esophageal Candidiasis: Fluconazole 200-400 mg/d PO (or 150 mg tab x 2-3 times/day), or Itraconazole 200 mg/d PO for 14-21 days

- Vulvovaginal Candidiasis :

Clotrimazole 100 mg or Miconazole 100 mg as vaginal suppository, 1 suppository every night for 7 days or

Clotrimazole 200 mg vaginal suppository, 1 suppository every night for 3 days or

Clotrimazole 500 mg vaginal suppository, 1 suppository as single dose or

Nystatin 100.000 IU as vaginal suppository, 1 suppository/day for 14 days, or

Itraconazole 100 mg OR 2 tabs/day for 3 consecutive days, or

Fluconazole 150 mg single dose (may not be effective in advanced disease)

**Consolidation therapy:** is given only for cases with multiple recurrences because of the risk of resistance.

- Fluconazole 150-200 mg or Itraconazole 200 mg once a day (qd) for 14 days

**Special considerations in children:** The dosage by weight of the drugs for children is as followed:

- Esophageal Candidiasis: Ketoconazol 5 mg/kg PO 1 - 2 times per day x 2-3 weeks, or Fluconazole 6mg/kg in first day, then 3 - 6mg/kg/day PO x 2-3 weeks.

- Invasive candidiasis: Amphotericin B 0.5 - 1.5 mg/kg/day x 2-3 weeks

**Special considerations in pregnancy**

- The risk of vaginal candidiasis is increased in pregnant women. Single dose of fluconazole or short course of itraconazole does not increase the risk of teratogenicity for the fetus.

- Women with esophageal candidiasis in the first trimester of pregnancy should be treated with amphotericin B. Do not give long term fluconazole or itraconazole because of the potential teratogenicity.

## 1.2. Penicilliosis

**Clinical manifestations:** Penicilliosis often occurs when the patients are in advanced stage of immunodeficiency with the TCD4 cell count  $<200/\text{mm}^3$ . Manifestations:

- Fever, lymph node enlargement, hepatosplenomegaly, weight lost, anemia.

- Skin lesions: necrotic papules with central umbilication, distributed mainly in the head, face, upper trunk and upper arms or spread all over the body.

### ***Laboratory Diagnosis***

- Clinical diagnosis if patients present with fever and characteristic skin lesions
- Skin, bone marrow or lymph node smear for the fungus, if possible
- Culture of blood and the above specimens in Sabborraud media at 25° - 37°C.
- Skin biopsy

### ***Treatment***

#### ***Initial treatment***

- *Preferred regimen:* Amphotericin B 0.6-1mg/kg/d IV for 6-8 weeks, or itraconazole 200mg bid for 2 months, then 200mg qd in following months, or
- *Combination therapy:* Amphotericin B 0.6mg/kg/d IV for 2 weeks, then itraconazole 200mg qd for another 10 weeks.

***Long-term maintenance therap:*** Itraconazole 200mg/d lifelong. Can be stopped if the patient is on HAART and has the TCD4 count > 200 cells/mm<sup>3</sup> x > 6 months.

***Special considerations in pregnancy:*** Do not use itraconazole for pregnant women in the first trimester because of the potential teratogenicity; give amphotericin B instead.

### **1.3. Cryptococcal Meningitis**

**Clinical manifestations:** The disease is seen primarily in patients with severe immunodeficiency, TCD4 cell count is <100/mm<sup>3</sup>.

- Meningitis: fatigue, fever, persistent headache along with nausea, vomiting, altered mental status, seizures, coma; meningeal signs are often mild; visual and hearing impairment can present, etc.
- Skin manifestations: nodules-papules, often with central necrosis; ulcers, pustules.
- Pneumonia : disseminated interstitial pneumonia
- Other organs, s.a. bone, kidney, liver, lymph node, can be involved

### **Diagnosis**

- Lumbar puncture: The CSF is often clear, opening pressure is high. Protein and glucose abnormalities may be minimal. Cell count is often only mildly elevated, mostly lymphocytes. India ink preparation of CSF, look for fungal cells. Fungal culture of CSF.
- Skin biopsy, microscopy and culture for the fungus
- Detection of cryptococcal antigen in serum

## **Treatment**

**Induction therapy:** Given to severe cases of cryptococcal meningitis (the patient is in altered mental status, has symptoms of brain edema, the fungus is visualized in the CSF smear, etc.)

- Preferred regimen: Amphotericin B 0.7 mg/kg/d + flucytosine 100 mg/kg/d x 2 weeks, or
- Amphotericin B 0.7 mg/kg/d x 2 weeks

### **Consolidation therapy:**

- Fluconazole 400-800mg/day x 8 weeks
- Mild cases can be placed on oral fluconazole from the beginning.

### **Maintenance therapy:**

- Fluconazole 200-400 mg/d, or Itraconazole 400 mg/d.
- Discontinue the therapy if the patient is on HAART and the TCD4 cell count is > 200/mm<sup>3</sup> for greater than 6 months.

**Special considerations in children:** Cryptococcal disease is seen less frequently in children, more common in children > 6 years of age. Localized lung disease is rare, manifest with persistent fever, hilar lymphadenopathy, focal or diffuse infiltrations in the lungs. The diagnosis and treatment are the same as in adults.

**Special considerations in pregnancy:** Do not use fluconazole or itraconazole for pregnant women in the first trimester because of potential teratogenicity; give amphotericin B. Flucytosine can be used in the first trimester if indicated.

## **1.4. *Pneumocystis jiroveci* (formerly *P.carinii*) Pneumonia (PCP):**

**Clinical manifestations:** Commonly seen in severe immunodeficiency, TCD4 count <200/mm<sup>3</sup>.

- *P.jiroveci* causes disease primarily in lungs; the disease often has subacute onset (days to weeks);
- The major signs and symptoms include dry cough, dyspnea with cyanosis, fever. Rales can be heard over the lungs, but normal breath sounds can be found.

### **Diagnosis:**

- Diagnosis is based on the clinical manifestations and lesions on chest X-ray
- Typical chest X-ray lesion: diffuse interstitial infiltration. Pneumothorax or normal chest X-ray may be seen.
- Confirmation of diagnosis: Look for *P. carinii* in smear from sputum (induce sputum to increase the sensitivity), BAL fluid. Staining methods: Giemsa, silver impregnation, immunofluorescent.

**Treatment:**

- **Preferred regimen:** TMP 15mg/kg/day + SMX 75mg/kg/day PO x 21 days.
- **Alternative regimens:** TMP 15mg/kg/day + Dapsone 100mg/day PO x 21 days, or Clindamycin 600mg IV every 8 hrs or 300-450mg PO every 6 hrs + Primaquin 30mg x 21 days.  
Severe cases with respiratory failure (dyspnea, cyanosis,  $PO_2 < 70$  mm Hg), Give prednisolone 40mg PO b.i.d on days 1-5, 40mg/day on days 6-10, then 20mg/day on days 11-21.
- Longterm maintenance therapy: starts right after completion of treatment for acute PCP and continues lifelong. Can be stopped when the patient is on HAART and the TCD4 count is  $> 200$  cells/mm<sup>3</sup> x  $> 3$  months. Regimen: TMP-SMX PO 960 mg qd.

**Special considerations in children:**

- *Pneumocystis carinii* pneumonia is the most common OI in HIV-infected children, usually occurs at the age of 3-6 months, but can start as early as 3-6 weeks of age. The disease is often severe with high mortality.
- Clinically, the disease may have either acute or subacute onset. The child often has fever, cough, tachypnea, cyanosis; physical examination reveals rales in bases of the lungs.
- Laboratory analyses often show moderate to severe hypoxia (low  $PaO_2$ , alveolar-arterial oxygen gradient  $> 30$  mm Hg), high WBC, LDH  $> 2$  times normal value
- X ray: diffuse interstitial infiltrations. Lobar infiltrations, milliary lesions or normal chest X-ray can be seen.

**Treatment:**

- **Preferred regimen:** TMP - SMX 15-20mg/kg/day (by TMP) divided 3-4 times a day for 21 days
- **Alternative regimen:** Clindamycin 20-40mg/kg/day in 4 divided doses IV + Primaquine 15- 30mg/day
- Supportive treatment with steroids for cases with respiratory failure,  $SpO_2 < 70\%$ . Recommended dosing: Prednisolon 2 mg/kg/day in 2 divided doses x 5 days, then 1mg/kg/day x 5 days, then 0.5mg/kg/day from day 11 to day 21; stop treatment according to the patient's condition.

**Special considerations in pregnancy**

- If the woman is treated with TMP-SMX or dapsone near the time of delivery, the neonatal room should be notified and the newborn should be followed for early detection of hyperbilirubinemia and kernicterus.
- Pneumonia in pregnancy can cause pre-term labor and pre-term delivery.

## **1.5. Aspergillosis**

**Clinical manifestations:** The disease often occurs in patients with severe immunodeficiency and AIDS.

- The fungi usually cause lung infection, but also sinusitis, infection of the external ear tubes, keratitis, infection of the brain, liver, kidney and other organs.
- Manifestations: cough, sometimes with hemoptysis, chest pain, dyspnea, night sweats, pain above sinus area and swelling of the face. The patient quickly deteriorates.

### **Diagnosis:**

- Detection of fungi in BAL fluid or infected tissue.
- Bronchoscopy shows pseudomembranous plaques
- chest X-ray and CT-scanner of lungs show disseminated lesions
- Fungal culture
- Biopsy and histology.

### **Treatment:**

- Amphotericin B 1.0-1.5mg/kg IV, or
- Itraconazole 200mg tid for patients with mild or moderate infection, or
- Combination of the two drugs for severe cases, especially brain infection.

***Special considerations in pregnancy:*** Do not give azole drugs for women in the first trimester of pregnancy, use amphotericin B.

## **1.6. Histoplasmosis**

**Clinical Features:** Disseminated histoplasmosis often occurs when the TCD4 < 200 cells/ml

- Symptoms are non-specific and often similar to other opportunistic infections, including prolonged fever, wasting, diarrhea and hepatosplenomegaly.
- The lungs are commonly involved with symptoms of shortness of breath and findings of pulmonary nodular infiltrates +/- hilar lymphadenopathy.
- Rare symptoms include encephalitis, acute meningitis, P.O. and anal ulcers, or gastrointestinal tract involvement.
- Skin lesions are also occasionally present, usually manifesting as macular papular eruptions and petechiae.
- Hepatosplenomegaly, lymphadenopathy
- Laboratory findings: Findings are non-specific and may include anemia, leukopenia, thrombocytopenia, elevated LFTs,

### **Laboratory Diagnosis**

- Cultures of sputum, bone marrow, lymph node, blood, CSF or any skin lesion. Media used: brain-heart infusion agar with source of blood plus antibiotics and cycloheximide. Incubate cultures for 6 weeks at 30 degrees C. More than 90% of cultures exhibit growth within 7 days. Sensitivity of culture is variable, but improves with increased amount of specimen.
- Histopathology: The pathogenic fungus may be visualized on PAS, Gomori methenamine silver and less often with Wright-Giemsa staining.

## **Treatment**

### ***Initial treatment***

#### Meningitis or other CNS involvement:

Amphotericin B 0.7-1.0 mg/kg/day until patient has received a total course of 30-35 mg/kg. Note: Itraconazole does not cross blood-brain barrier and should not be used.

#### Severe symptoms: (no CNS symptoms, but hemodynamic instability)

Amphotericin B 0.7-1.0 mg/kg/day until symptoms resolved followed by Itraconazole 400 mg/day for 6 months.

**Maintenance therapy:** Lifelong suppression with itraconazole 200 mg/day to prevent relapse.

***Special considerations in pregnancy:*** Do not use fluconazole and itraconazole for pregnant women in the first trimester because of the potential teratogenicity; use amphotericin B.

## **II- PARASITIC INFECTIONS**

### **2.1- Toxoplasma encephalitis:**

**Clinical manifestations:** The disease often occurs in severe immunodeficiency stage (TCD4<100 cell/mm<sup>3</sup>)

- Patients often present with signs and symptoms of focal neurological deficits, s.a. hemiparesis, cranial nerve palsy, aphasia; manifestations of brain edema (headache, altered consciousness, convulsions);
- Sign of an infection process: fever, etc.
- Patients with toxoplasma myelitis can present with paralysis, bladder problems.
- Rare forms of toxoplasmosis: uveitis, pneumonia..

#### **Laboratory diagnosis:**

- *CT Scanner of Brain with double-dose contrast:* multiple ring-enhancing lesions sized <2cm in diameters distributed in both hemispheres.
- *Magnetic Resonance Imaging* permits to detect the brain lesions with high sensitivity.
- *Serology:* to detect IgG anti-toxoplasma antibody. Negative tests are seen in patients with abnormalities of B cell function.
- *CSF:* non-specific abnormalities; positive toxoplasma IgG antibody.

- *Biopsy of brain lesions* is indicated only in rare instances when differential diagnosis with CNS lymphoma is needed (the patient has single lesion in the brain, not responding to anti-toxoplasma treatment).

**Treatment:**

Treatment should be timely. In case no laboratory diagnosis and imaging investigations available, the response to treatment can be used as support for diagnosis.

***Induction Therapy:***

- *Preferred Regimen:* Pyrimethamine 200mg loading dose, then 50-75mg/day PO + folic acid 10mg/day PO + sulfadiazine loading dose 2-4g, then 1-1.5g x qid (not exceeding 4g/day), for 3-6 weeks. (Folic acid is given to minimize the toxic effect of pyrimethamine).
- *Alternative Regimen:* is indicated when the preferred drugs are not available, or when the patients not tolerate sulfadiazine or develop side effects to these drugs (allergic reactions, crystalluria, etc).

TMP-SMX; dose by TMP is 10mg/kg/day, in 3-4 divided doses.

Pyrimethamine + clindamycin 600mg/6h, or:

Pyrimethamine + TMP-SMX (5mg/kg/6h by TMP), or:

Pyrimethamine + clarithromycin 1g/12h

Patients often improve clinically within 1 week. It often takes 2 weeks for the lesions on the CT-scanner or MRI to improve. If the patient does not respond to antitoxoplasma regimens, other alternative diagnoses should be considered (e.g. TB meningoencephalitis, CNS lymphoma, HIV associated encephalitis, etc).

***Maintenance therapy:*** Starts after induction phase, by one of the following regimens:

- Pyrimethamine 25-50mg/day + acid folic 10-25mg/day + sulfadiazine 1g/6hrs, or:
- Pyrimethamine 25-50mg/day + folic acid 10-25mg/day + clindamycin 300-450mg/6-8hrs, or:
- Pyrimethamine + sulfadoxin (Fancidar) 1 tablet x 3 times/week.

The maintenance therapy can be discontinued if patients are on HAART and have immune reconstitution with the TCD4 cell count of >200/ $\mu$ L for  $\geq$  6 months

***Special considerations in children:*** Toxoplasma infection in children can occur during intrauterine period (congenital toxoplasmosis) or after birth. Early symptoms of toxoplasmosis: fever, sore throat, myalgia, lymphadenopathy, rash, hepatosplenomegaly; late symptoms: encephalitis, fever, altered mental status, retinal lesions.

**Treatment:**

- Congenital infection: pyrimethamine 2 mg/kg/day PO QD x 2 days, followed by 1 mg/kg/day PO QD for 2-6 months, followed by 1 mg/kg/day PO three times per week PLUS sulfadiazine 100 mg/kg/day PO divided b.i.d PLUS acid folinic 10-25 mg PO QD. Total duration of treatment should be determined by a doctor experienced in toxoplasmosis.

- Acquired toxoplasmosis:

*Preferred regimen:* Pyrimethamine PO, loading dose 2mg/kg/day x 3 days, then 1mg/kg/day + Folinic acid PO 10-25mg QD + Sulfadiazin PO, 120 mg/kg/day divided QID x 3-6 wks.

*Alternative regimen:* Pyrimethamine + clindamycin

*Note:* TMP-SMX has not been tested in children with toxoplasmosis.

*Maintenance therapy:* starts right after initial therapy, for lifelong, with one of the following regimens: Pyrimethamine 1mg/kg/day + acid folinic 5 mg/kg t.i.w + sulfadiazine 85-120 mg/kg/day divided BID or QID or Pyrimethamine + clindamycin + acid folinic

### ***Special considerations in pregnancy***

- The neonatal room should be notified about the use of TMP-SMX or sulfadiazine in the mother near the time of delivery for early detection of hyperbilirubinemia and kernicterus in the newborn.
- Pregnant women with primary toxoplasmosis have high risk of transmitting the infection to the fetus; the risk of transmission in reactivation of maternal infection is lower. Ultrasound examination of the fetus should be done to detect hydrocephalus, cerebral calcifications and fetal growth retardations for pregnant women with toxoplasmosis.

## **2.2- Parasitic diarrheas**

**Causes:** Cryptosporidia, Microsporidia, Isospora.

**Clinical manifestations:** manifestations vary from self-limited disease to severe and prolonged diarrhea leading to death. The more suppressed the immunodeficiency, the more severe and prolonged the disease.

Major signs and symptoms:

- Prolonged diarrhea (for months); profuse watery stool, up to several liters per day; Dull abdominal pain, nausea, vomiting
- Malnutrition, malabsorption
- Cholangitis can be present (cryptosporidia), keratitis (microsporidia)

### **Laboratory diagnosis:**

- Stool microscopy reveals no RBC, WBC (non-invasive diarrhea)

- Stool examination by formalin-ether concentration method with modified acid-fast staining for cryptosporidia and trichrome staining for microsporidia and isospora. Other methods of staining with giemsa, safranin-blue methylene, silver staining can also be used.
- Intestinal mucosa biopsy and electron microscopy when possible to find cryptosporidia attached to villi of epithelial cells.

**Treatment :** Provide adequate water and electrolyte replacement and nutrition support; antidiarrheal drugs like loperamide and NSAIDs can also be used. Effective HAART with maintaining good immune status of the patients is the prophylaxis and treatment for parasitic diarrheas. Following regimens can be used in cryptosporidia infection with certain effectiveness:

- Cryptosporidia: Paromomycin 500mg tid or 1000mg bid PO during meal for 14-28 days, then 500 mg bid; can be combined with azythromycin 600mg qd in the first 4 weeks ; or Nitazoxanide 500mg bid
- Microsporidia: Albendazole 400-800mg/day PO bid for at least 3 weeks; or Metronidazole 500mg PO tid; or Atovaquone 750mg PO bid with meals; or Thalidomide 100mg/day. Patients with microsporidial keratitis can be treated with topical fumagillin solution, combined with P.O. albendazole.
- Isospora: TMP-SMZ PO 2 double-strength tablets b.i.d or 1 double-strength tablet three times a day (t.i.d) for 2-4 weeks; *or* Pyrimethamine PO 50-75mg/day + folic acid 5-10mg/day for 1 month; then suppressive treatment with TMP-SMZ PO 1-2 double-strength tablets b.i.d or t.i.w; or Pyrimethamine 25mg + sulfadoxine 500mg/week (1 Fansidar tablet/week)

***Special considerations in pregnancy:*** Do not use thalidomide and albendazole for pregnant women. Notify neonatal room about the use of TMP-SMX in mother near the time of delivery for early detection of hyperbilirubinemia and kernicterus in the newborn.

***Special considerations in children***

- Treatment of cryptosporidial diarrhea: Azithromycin 10mg/kg PO first day, followed by 1-5 mg/kg/day for 5 - 10 days with/without paromomycin 25-35 mg/kg/day PO in 2-3 divided doses may help symptoms.
- Treatment of isospora diarrhea: TMP-SMX 20mg/kg/day x 10-21 days

**2.3. Leishmaniasis**

**Clinical features:** HIV infected persons are at risk of visceral leishmaniasis when the TCD4 cell count is <200/mm<sup>3</sup>.

*Visceral leishmaniasis:*

- Prolonged fever, anorexia, weight loss, massive hepato- and splenomegaly, lymphadenopathy, abdominal pain, diarrhea.
- Atypical presentations are more common in patients with profoundly depressed TCD4 counts. These patients may have lack of splenomegaly as well as involvement of lungs, pleura, P.O. mucosa, esophagus, stomach, small intestine, skin and bone marrow.

- Laboratory findings are non-specific and include: pancytopenia, hypergammaglobulinemia, hypoalbuminemia, elevated transaminases, hyperbilirubinemia.

*Cutaneous lesions:* macules, papules, plaques, nodules or ulcers, gummas; locations: face, ears, extremities or the whole body, primarily in open skin.

**Laboratory diagnosis:**

- Parasites are occasionally found in circulating leukocytes on peripheral blood smear. Blood cultures may be positive in HIV infected individuals.
- Biopsy and staining of any involved organ with May Grunwald-Giemsa staining may reveal granulomatous inflammation with intracellular amastigotes.
- Splenic biopsy is most sensitive though there is risk for rupture. Bone marrow aspiration is the next most sensitive and safest. Skin biopsy should be performed if lesions are present and diagnosis is suspected.
- Culture: Organisms grow at 26-28 degrees C on Novy-McNeal-Nicolle media or Schneider's media containing fetal calf serum. Cultures should be held for 4 weeks.

**Treatment:**

- Antimony (stibogluconate or meglumine antimonate) 20 mg/kg/day intramuscularly (IM) or intravenously (IV) in 2 divided doses for 28 days.
- Amphotericin B 0.7 mg/kg/day for 28 days.
- Patient should be monitored closely for side effects of both Antimony and Amphotericin. The 2 drugs should not be given together.

**Maintenance therapy:**

- Stibogluconate or meglumine antimonite 20 mg/kg IV or IM once per month.
- Other drugs such as liposomal amphotericin B are being studied.

**Special considerations in pregnancy:** Do not use antimony compounds for pregnant women, as they have not been evaluated for the safety. Use amphotericin B.

### III- BACTERIAL INFECTIONS

#### 3.1. Tuberculosis (*Mycobacterium tuberculosis*):

**Clinical manifestations:** Tuberculosis can occur at any stage of HIV infection and the clinical manifestations depend on the level of immunodeficiency.

**Pulmonary tuberculosis:**

- In the early stage of HIV infection, when the immune status is still relatively normal, the patients often present with fever, cough, fatigue, weight loss, night sweats.
- In the late stage of HIV infection with immunosuppression, the patients do not have much coughing and present mainly with fever and weight loss.

**Extra pulmonary tuberculosis:** Commonly seen in patients with low TCD4 count. Patients often present with chronic fever, weight loss, and the signs and symptoms from organs involved.

- TB lymphadenitis: often starts abruptly. The affected lymph nodes are often firm, localized symmetrically on both sides, persist for long time.
- TB pleuritis: cough, chest pain, pleural effusion...

- TB pericarditis: chest pain, pericardial effusion.
- TB meningitis: subacute onset of headache and fever; meningeal signs, mental disturbances and focal neurologic deficits if the disease has prolonged course.
- TB peritonitis: abdominal pain, ascites.
- Gastrointestinal tuberculosis: abdominal pain, diarrhea or ileus, bloody stool, mass palpable in the abdomen.
- Miliary Tuberculosis: fever, fatigue, weight loss; the respiratory symptoms are not prominent; there may be signs and symptoms from other organs such as gastrointestinal tract, central nervous system.
- Rare forms of TB: TB spondylitis (Pott's disease), brain tuberculoma, TB abscess of chest wall...

**Laboratory:**

- Chest X-ray: radiographic appearance varies with the stage of immunodeficiency.
  - In relatively immunocompetent stage: infiltrations or cavitations in upper lobes.
  - In immunosuppressed stage: diffuse or nodular-reticular infiltrations in lower lobes similar to miliary TB; hilar or mediastinal lymphadenopathy.
  - Other findings on chest X-ray: pleural and pericardial effusions.
  - CXR may be normal in stages of advanced immunosuppression.
- Sputum smear for AFB: The Sputum AFB is usually positive in patients with relatively preserved immunity and typical pulmonary lesions. In stages of advanced immunosuppression, the sputum smear may be negative even with active pulmonary disease.
- Bronchoscopy and BAL; staining of bronchoalveolar fluid for AFB.
- Lymph node aspiration or biopsy with AFB staining, lymph node cytology or histology to look for TB characteristic lesions.
- Analysis of CSF, pleural, or pericardial fluids when these organs are affected. Do biochemistry, cytology and bacteriology (smear, PCR, ELISA) for diagnosing TB.
- Culture of sputum and other specimens for *M.tuberculosis* and antibiotic sensitivity testing, if possible.
- Skin Mantoux test: can be negative in severely immunosuppressed or severe TB patients, and of little diagnostic value when not reactive.
- Brain CT scanner and others imaging diagnosis when necessary and possible.

**Treatment:**

Treatment for tuberculosis in HIV infected patients is generally not different from non-immunosuppressed patients. Specific considerations are:

- All TB/HIV patients should be referred to TB program for consultation and placed on DOT;

- Thiacetazone is not used because of multiple side effects;
- Streptomycin is still effective for TB treatment but is not recommended in the settings with poor disinfection facilities to avoid HIV transmission through contaminated needles and syringes;
- The duration of treatment can be prolonged in severe extrapulmonary or disseminated TB such as millary TB, pericarditis, meningitis and spondylitis with neurological complications, depending on the severity of the disease and can be as long as 18 months;
- Special cautions should be exercised when giving anti-TB and ARV drugs due to possibilities of drug interactions, especially between rifamycin and NNRTIs and PIs (see Annex 8: Drug Interactions of ARVs);
- Monitor the response to treatment to detect drug resistance and monitor after treatment completion to detect relapse or re-infection.

**Treatment for New TB patients:**

- **Regimen: 2SHRZ/6HE:** use 4 drugs Streptomycin (S/SM), Isoniazid (H/INH), Rifampicin (R/RMP) and Pyrazinamide (Z/PZA) daily for first 2 months, then 2 drugs Isoniazid and Ethambutol (E/EMB) daily for another 6 months.

- **Indication:** All new TB patients.

• **Re-Treatment:**

- **Regimen: 2 SHRZE / 1 HRZE / 5 H<sub>3</sub>R<sub>3</sub>E<sub>3</sub>.** Use 5 drugs S, H, R, Z, E daily for the first 2 months; in the third month use 4 drugs H, R, Z, E daily (without S); for the next 5 months use 3 drugs H, R, E three times a week.

- **Indication:** This regimen is used for patients who fail or relapse after initial TB Regimen.

**Table 3: Optimal Dose of Essential anti-TB Drug**

Drugs	Daily dose (mg/kg)	Intermittent Dose(mg/kg)	
		3 times/week	2 times/week
Isoniazid	5 (4-6)	10 (8-12)	15 (13-17)
Rifampicin	10 (8-12)	10 (8-12)	10 (8-12)
Pyrazinamide	25 (20-30)	35 (30-40)	50 (40-60)
Ethambutol	15 (15- 20)	30 (25-35)	45 (40-50)
Streptomycin	15 (12-18)	15 (12-18)	15 (12-18)

*Special considerations in children*

TB infection can occur at any time during the course of HIV infection. Small children are at higher risk of being infected and having disseminated TB.

### **TB Treatment for Children:**

Use 3 drugs H, R, Z daily in first 3 months, followed by 2 drugs H, R for another 4 months. For severe forms of TB like meningitis, miliary TB, bone and joint TB Streptomycin can be added in first 2 months of “induction phase“

### ***Special considerations in pregnancy***

- Chest radiographs with abdominal shielding is relatively safe for the fetus.
- Pulmonary and extra-pulmonary TB during pregnancy can result in pre-term birth, low birth weight and fetal growth retardations, especially when the patient is not treated and the disease persists until late period of pregnancy.
- INH, RFM, PZA and EMB can be used safely in pregnancy. Monitor liver functions for patients on INH. Neonates born to mothers who have been treated with RFM during pregnancy may have hemorrhagic manifestations, and therefore need prophylactic treatment with vitamin K 10mg after birth.
- Do not use streptomycin and kanamycin for pregnant women because of toxicity to VIII cranial nerve of the infants, causing congenital deafness.

## **3.2. Infection with Atypic Mycobacteria**

***Clinical manifestations:*** The disease often occurs in the late stage of HIV/AIDS disease, when the TCD4 cell count is <100 cell/mm<sup>3</sup>.

- Major signs and symptoms: Fever, weight loss, night sweats; lymphadenopathy, abdominal pain, diarrhea; manifestations of liver and lungs' involvement.

### ***Laboratory diagnosis:***

- Smear from sputum, lymph node and bone marrow aspiration or stool for AFB (differential diagnosis with TB).
- Blood culture and culture of other specimens on specific media for isolation of mycobacteria
- Chest X-ray: interstitial infiltrations in lower lobes of both lungs
- Increased alkaline phosphatase

***Treatment:*** long-term treatment (at least 1 year) by one of the following regimens. Discontinue if the patients are on treatment with ARV with the TCD4 cell count >100 cell/mm<sup>3</sup> for 3-6 months.

***Preferred Regimen:*** Clarithromycin PO 500mg bid + Ethambutol PO 15mg/kg/day

***Alternative Regimen:***

- . Azithromycin PO 600mg/day + Ethambutol ± Rifabutin PO 300mg/day, or:
- . Azithromycin PO 600mg/day + Ethambutol in combination with Amikacin IV 10-15mg/kg/day or Ciprofloxacin 500-700mg bid

### ***Special considerations in children***

- . Major symptoms: prolonged fever, failure to thrive, night sweat, anemia, hepatosplenomegaly, chronic diarrhea, isolated lymphadenopathy or pulmonary disease.
- . If AFB are found in lymph node aspiration or biopsy, the differentiation should be made from TB.
- . Treatment is with combination of 3-4 drugs for long time. The preferred regimen is azithromycin 10-12 mg/kg/day PO QD, or clarithromycin 7.5-15 mg/kg/day PO divided bid, with ethambutol 15-25 mg/kg/day PO QD, and rifamycin 10-20 mg/kg/day PO QD.

### **3.3. Streptococcus pneumoniae infection**

#### ***Clinical manifestations***

- Pneumonia: cough, fever, chest pain, dyspnea, cyanosis.
- Otitis media: high fever, ear pain, vomiting.
- Sinusitis: fever, headache, pain above sinus areas, stuffiness.
- Bacteremia: high fever with chills, severe general condition, altered mental status.
- Meningitis: fever, vomiting, neck stiffness, convulsion, obtundation.

#### ***Laboratory diagnosis***

- Chest X-ray: pneumonia, commonly with lobar involvement
- High WBC and neutrophil count.
- Blood culture
- Culture of blood, sputum, ear discharge or CSF for pneumococci.
- Gram stain of above fluids to visualize elongated, gram-positive diplococci.

#### **Treatment**

- For penicillin-sensitive pneumococci: Penicillin G 400,000 IU/kg IV q6h for 7 - 10 days.
- For penicillin-resistant pneumococci: Cefotaxim 200 - 300mg/kg q8h IV, or ceftriaxone 50-80 mg/kg/day IV in 2 divided doses

### **3.4. Staphylococcus aureus infection:**

**Clinical manifestations:** S.aureus infection is commonly seen in IDUs. Major manifestations include:

- Skin infection: folliculitis, pustules, furuncles, etc; fever can present
- Sepsis: high fever, chills, ill appearance of the patient

- Myositis, muscle abscesses, arthritis, osteomyelitis: patients present with fever; the involved muscle is swollen, painful, erythematous and hot on palpation; infected joints are swollen, painful and the joint's movement is limited
- Pneumonia, lung abscesses, empyema: fever, cough, dyspnea, crackles, friction rub, etc.
- Meningitis, brain abscesses, thrombophlebitis, epidural abscesses: fever, headache, focal deficits, paralysis and disfunction of bladder, etc.
- Endocarditis: fever with chill, embolism signs of extremities, anemia, heart murmurs

**Diagnosis:**

- Culture of blood, pus, sputum and other specimens to recover *S.aureus*.
- Gram stain of sputum, abscess pus, pleural fluid: detection of gram positive cocci in clusters
- Chest X ray: multiple abscesses, pleural effusion
- Echocardiography: valvular vegetations, pericardial effusion, myocardial abscesses, etc.
- Brain CT scanner, spine MRI if any suspicion of CNS complications

Treatment: best based on the antimicrobial sensitivity testing. The dosage of antimicrobials, route of administration and duration of treatment depend on the site and severity of infection.

*Preferred regimen:* anti-staphylococcal penicillins (methicillin, oxacillin..) or first generation cephalosporins (cephazolin, cephalothin..) IV; average dose is 100mg/kg/d + an aminoglycoside (gentamicin, netilmycin..).

PO drug: cephalexin 500mg x 4 times per day (for mild infection only, not for bacteremia)

*Alternative regimens:* used for methicillin-resistant *S.aureus*. Vancomycin 1g bid IV plus an aminoglycoside (gentamicin, netilmycin..)

***Special considerations in pregnancy:*** Do not use aminoglycosides as these drugs can cause congenital deafness in the infants.

**3.5. Bacterial diarrheas:**

**Common causes:** Salmonella, Shigella, Campylobacter and some other enteric bacteria

**Clinical manifestation:**

- Fever, diarrhea with watery or bloody-mucous stool; the patients may present with abdominal pain and tenesmus.
- The disease is often severe, has prolonged course and frequently comes along with bacteremia; septic metastatic foci can be found in lungs, joints, liver, bone marrow.
- The patients may become chronic carriers and are prone to relapses.

**Diagnosis:**

- . RBC and/or WBC on stool microscopy (invasive diarrhea)
- . Blood culture

- . Stool culture
- . Culture of pus or other pathologic fluids

**Treatment:**

- *Salmonella*: Ciprofloxacin 500mg bid or Ofloxacin 200-300mg/d bid PO for at least 14 days. *Alternative regimen*: 3<sup>rd</sup> generation cephalosporins IV (e.g. ceftazidime, cefoperazone, etc.) 50mg/kg/d for at least 14 days for patients with fluoroquinolone allergy or intolerance.
- *Shigella*: ciprofloxacin 500mg bid OR x 5 days. *Alternative regimen*: ceftriaxone 50mg/kg/d x 5 days IV, given to patients with fluoroquinolones allergy or intolerance.
- *Campylobacter*: erythromycin 500mg x 4 times/day for 5-7 days or ciprofloxacin 500mg bid for 5-7 days.
- In case no cause of diarrhea can be detected, empiric treatment with ciprofloxacin or another fluoroquinolone can be given. Follow the response to treatment (fever, diarrhea) and follow the patient after the treatment to detect chronic carrier state and relapse. Patients with septicemia or chronic carrier state need prolonged treatment (for weeks) or maintenance therapy with ciprofloxacin 500 mg bid (infection with salmonella).

***Special considerations children and in pregnancy***

The fluoroquinolones can cause arthropathy in animal fetus and immature animals in experimental studies. However, in practice, similar effects have not been found in children treated with quinolones or infants with intra-uterine quinolone exposure. The fluoroquinolones can be used in children and pregnant women if the causative strains of salmonella are resistant to other antibacterials.

**3.6. Klebsiella pneumoniae infection**

**Clinical manifestations:** Fever, pneumonia, lungs' abscesses, purulent pleural effusion, septic shock, urinary and biliary tract infections

**Diagnosis:**

- Sputum smear: Gram negative rods with capsules
- Isolation of Klebsiella from sputum, blood and other specimens
- Chest X-ray to look for lungs' lesions (infiltrations, lungs' abscesses, pleural effusion)

**Treatment:** Choose antimicrobials on the basis of sensitivity testing. The dosage and duration of treatment depends on the site of infection and the response to treatment.

*Preferred regimen*: 3<sup>rd</sup> generation cephalosporins (e.g. ceftazidime) IV; average dosage of 100mg/kg/day ± an aminoglycoside (e.g. amikacin IM 500-1000mg/day).

*Alternative regimen*: ciprofloxacin PO 500-750mg x b.i.d.

***Special considerations in children and in pregnancy***: See Salmonellosis.

**3.7. Syphilis**

***Clinical manifestations***

- Primary syphilis: characteristic chancre, accompanied by local lymphadenopathy. Multiple chancres with extensive swelling and pain may be seen.
- Secondary syphilis: protean manifestations, including skin eruption of macular, papular character, sometime with crusts, involving palms and soles; condyloma lata in ano-genitalia; plaque lesions in anogenital mucosae; fever; alopecia; generalized lymphadenopathy; meningitis, etc.
- Latent syphilis: patients are asymptomatic, but the serology is positive.
- Tertiary syphilis: gummatous syphilis, neurosyphilis, cardiovascular syphilis, and may involve other organs. Neurosyphilis often occurs early, may be asymptomatic but with changes in CSF; patients often have concomitant uveitis.
- Congenital syphilis: vesicular and bulous skin eruption, osteo-chondroititis and periostitis, hepatosplenomegaly and lymphadenopathy, jaundice, anemia, and other abnormalities, such as lip and hard palate defects.

### ***Diagnosis***

- Darkfield microscopy of the materials from the lesions of primary and secondary syphilis to visualize the syphilis spirochetes.
- Serology analysis: RPR, VDRL. Quantitative assays should be done to assess the effectiveness of treatment. Patients with high suspicion of syphilis with negative serology should be evaluated by other analyses, such as biopsy, darkfield microscopy, or direct fluorescent antibody assay of the smear from the lesions.
- All patients with HIV/syphilis co-infection should have ophthalmologic and neurological examinations. Patients with neurological and/or ocular symptoms, patients with late latent syphilis and syphilis of unknown duration should have spinal tapping performed to rule out neurosyphilis. The CSF in neurosyphilis may have little changes (normal or slightly elevated protein, the cells are predominantly mononuclear). Neurosyphilis should be differentiated from HIV-related meningitis. Do VDRL, RPR with CSF; if false positive reaction is suspected, perform TPHA.

### ***Treatment***

- *Early syphilis* (primary and secondary syphilis, latent syphilis < 2 year): Benzathine penicillin G 2.4 MU, IM single dose in the thigh, with 1.2 MU at each site, or crystalline procaine penicillin G, IM 1.2 MU/day x 10 days.
- If the patient is sensitive to penicillin and is not pregnant: doxycycline 100mg PO bid x 15 days, or erythromycin 500mg, PO q.i.d x 15 days, or ceftriaxone 1g every day IM or IV x 8-10 days.
- *Late latent syphilis in adults*: Benzathine penicillin G 2.4 MU, IM, 1.2 MU at every thigh, every week x 4 weeks (total dose of 9.6 MU), or crystalline procaine penicillin G, 1.2 MU IM every day x 3-4 weeks.
- *Neurosyphilis*: Crystalline penicillin G 2 MU, IV every 4-6 hrs, total daily dose 8-12 MU x 3 weeks, or crystalline procaine penicillin G 1.2 MU, IM every day + Probenecid 500mg PO q.i.d x 3 weeks.

- *Syphilis in pregnant women*: Give the same regimens as for other adults above in all the period of pregnancy, except for doxycycline.  
If the patient is allergic to penicillin: Erythromycin 500mg PO q.i.d x 15 – 30 days
- *Congenital syphilis*:
  - Early congenital syphilis, aged < 2 years, normal CSF: benzathine penicillin G 50,000 U/kg IM single dose.  
Abnormal CSF: benzyl penicillin 50,000 U/kg IV or IM b.i.d x 10 days, or procaine penicillin G 50,000 U/kg x 10 days.
  - Late congenital syphilis, aged > 2 years: normal CSF – benzyl penicillin 30,000 U/kg IM single dose; abnormal CSF - benzyl penicillin 20,000 – 30,000 U/kg/day divided b.i.d x 14 days; or erythromycin 7.5 – 12.5 mg/kg PO q.i.d x 30 days if the patient is sensitive to penicillin.
  - The child also needs treatment when the mother has history of syphilis but has not been treated for, even if the child has negative serology and no symptoms, or the mother was treated with non-penicillin regimens.

## **8. Infection with Haemophilus influenzae type B**

### **Clinical manifestations:**

- Acute pharyngitis or pneumonia: cough, fever, dyspnea
- Otitis media (in older children): fever, pain over the ear, headache, vomiting
- Meningitis: fever, headache, vomiting, neck stiffness
- Septicemia: fever, toxic appearance, metastatic foci

### **Diagnosis:**

- Chest X-ray: Broncho-pneumonia
- CSF: bacterial meningitis, smear reveals Gram (-) bacilli
- Culture of blood, bronchial fluid, CSF.

### **Treatment:**

- Ampicillin 200 - 300mg/kg/day IV in 4 divided doses + Chloramphenicol 100mg/kg/day IV in 3 divided doses; or
  - Cefotaxime 200mg/kg IV every 8 hrs; or
  - Ceftriaxone 100mg/kg IV every 12 hrs
- Give treatment for 10 - 14 days.

## **IV. VIRAL INFECTIONS**

### **4.1. Herpes simplex infection:**

#### **Clinical manifestations:**

*Skin and mucosa manifestations*: vesicular eruptions in crops, quickly progressing to ulcerations; frequently localized in or around the genital organs, can be found in rectum and colon, oral cavity and perioral areas, occasionally spreading to esophagus causing

dysphagia, odynophagia; sometimes can expand to trachea and bronchi. The disease is generally more severe with frequent relapses compared with HIV-negative persons.

*Herpes encephalitis*: The manifestations are often nonspecific with focal symptoms of frontal-temporal lobe's involvement.

**Diagnosis:**

- Diagnosis based on the appearance of the lesions
- Tzanck preparation for gigantic cells; viral culture or fluorescent antibody test, PCR, if possible.

**Treatment:** Topical ointment with dyes' or antibacterial solutions to combat superinfection. Topical acyclovir is of limited effectiveness.

- Acyclovir 200mg 5 tabs/d for 5 -10 days for mild cases, or
- Acyclovir 400mg tid for 5 -10 days, or
- Acyclovir 5 mg/kg IV q8h for 10 days for severe cases, or
- Famciclovir 125 mg PO bid for 5 -10 days, or
- Valaciclovir 500mg PO bid for 5 -10 days, or
- Valaciclovir 1g bid for 10 days (primary HSV infection)

For acyclovir-resistant HSV: Foscarnet 40-60mg/kg IV q8h for 21 days.

For acyclovir and foscarnet resistant HSV: cidofovir IV.

**Prevention of relapse:** prolonged acyclovir 400 mg bid for frequently relapsing cases.

***Special considerations in pregnancy***

- Acyclovir and valacyclovir are safe for use in pregnancy. Use foscarnet only in case of severe HSV infection when the other drugs fail.
- Pregnant women with active or chronic genital HSV infection have the potential to transmit the virus to the fetus and neonate. Consider cesarean delivery for women with genital herpes at the onset of labor.

**4.2. Herpes zoster infection:**

**Clinical manifestations:** Varicella Zoster Virus disease may occur when the TCD4 cell count is still relatively high (300-500/mm<sup>3</sup>).

- Clustered vesicular eruptions with central crust, distributed within a dermatome, commonly on the chest, back and face, along the path of a nerve.
- The patient often experiences burning pain in affected area, sometimes persistent even after the lesions already resolve, what is also called postherpetic neuralgia. Fever may present.
- The condition is often difficult to treat and frequently relapsed. The lesions can spread on both sides and affect multiple areas of the body (disseminated zoster).

### **Diagnosis**

Clinical manifestations are often typical and there is no need for laboratory diagnosis.

### **Treatment**

Give topical dyes (methylene blue, millian) to combat superinfection. Topical antivirals are often not effective and can irritate the lesions. Systemic therapy is preferred and is best when given early in the course of illness, within 72 hours after the onset of the lesions

- *Preferred regimen:* Acyclovir 800mg PO x 5 times a day for 7-10 days, or Acyclovir 10 mg/kg IV q8h. This regimen should be given for disseminated cases, or cases with involvement of trigeminal nerve. The treatment should be continued until the lesions heal, usually 7-14 days.
- *Alternatives regimens:* Famciclovir 500mg tid for 7-10 days, or Valacyclovir 1g tid for 7-10 days.

For Acyclovir-resistant cases: Foscarnet 40mg/kg IV q8h for 2-3 weeks.

Prevention of relapse ( $\geq 1$  relapse per month): acyclovir 400mg b.i.d longterm.

***Special considerations in pregnancy:*** Pregnant women with chicken pox can transmit the virus to the fetus during first and second trimesters (risk of 0.4-2.2%), resulting in congenital infection in infants. Babies born to mothers with chicken pox within 5 days before and 2 days after delivery can develop perinatal chicken pox.

### **4.3. Cytomegalovirus infection:**

**Clinical manifestations:** Cytomegalovirus (CMV) disease often occurs when TCD4 < 50 cells/mm<sup>3</sup>.

- Retinitis: blurred vision, with black floating dark spots, progressing to blindness.
- Colitis: prolonged diarrhea, colic pain, weight loss, anemia, prostration.
- Esophagitis: odynophagia, increasing with hard food, chest pain or hiccup.
- Gastritis: epigastric discomfort, fever, stomach bleeding, diarrhea.
- Encephalitis: clinical diagnosis is difficult. The symptoms include headache, dementia, confusion and fever. The disease quickly progresses to death.
- Polyradiculopathy: lower limbs are commonly affected, urinary incontinence.

- Skin manifestations: The CMV perianal ulcers are usually severe and difficult to treat, unresponsive to acyclovir. Other skin manifestations include nodules, hemorrhagic lesions, ulcers and vegetations.

**Diagnosis:** Fundoscopy when retinitis is suspected.

Colon biopsy, CSF, skin lesions, blood for cell culture or PCR, histology

## **Treatment**

### Retinitis

- Ganciclovir intraocular implant every 6 months
- Ganciclovir IV, 7.5-10mg/kg/day in 2-3 divided doses for 14 consecutive days or longer if no clinical response
- Foscarnet can be given to treat retinitis. However the efficacy is limited. The dosage is 60mg/kg every 8 hours, if effective, give 60-120 mg/kg/day, or valganciclovir 900 mg po BID x 21 days
- Valganciclovir intraocular implant every 6 months + IV ganciclovir or oral valganciclovir as above.

Maintenance treatment:

- Ganciclovir 5-6mg/kg/day, 5-7 days per week or
- Valganciclovir 900 mg po QD or
- Foscarnet 90-120 mg/kg IV QD; or
- Ganciclovir intraocular implant every 6-9 months + ganciclovir 1-1.5 g PO t.i.d.

Esophagitis or colitis: Ganciclovir or Foscarnet IV as dosed above x 21-42 days until the symptoms resolve. Oral valganciclovir can be used if the symptoms are not severe. Give maintenance therapy only if patients relapse.

Meningitis: Can start with induction doses as per retinitis. Combine IV ganciclovir + IV foscarnet if symptoms develop while patient is receiving ganciclovir. Give lifelong maintenance therapy or until CD4 count is greater than 100 for more than 6 months if patient is on HAART.

### ***Special considerations in children***

- CMV infection in children can occur during intrauterine period (congenital infection) or after birth. CMV disease is often seen in small children, co-infection with PCP can cause severe respiratory disease, what responds poorly to anti-PCP therapy.
- Major manifestations of CMV disease in small children: retinitis, esophagitis, hepatitis, pneumonia, encephalitis, colitis; fever, failure to thrive, development delay, hearing loss; anemia, thrombocytopenia, increased LDH.
- Diagnosis: CMV culture from blood, tissue, urine; histology on broncho-alveolar lavage or pathology specimens for virus specific intranuclear inclusion bodies. Serology is less effective.

*Treatment:*

- Preferred regimen for disseminated disease and retinitis: Ganciclovir 10-15 mg/kg/day IV divided bid x 14-21 days, followed by 5-10 mg/kg/day x 5-7 days/week.
- Alternative regimen: Foscarnet 180 mg/kg/day divided t.i.d x 14-21 days, followed by 90-120 mg/kg/day
- Alternative regimen for CMV retinitis in children > 3 years old: Ganciclovir intraocular injection plus ganciclovir 90 mg/kg/day PO divided TID.
- Give lifelong maintenance therapy with ganciclovir 5 mg/kg/day IV QD after disseminated disease. For maintenance therapy after CMV retinitis, an alternative regimen is intraocular ganciclovir every 6-9 months combined with ganciclovir 90 mg/kg/day PO divided TID.

***Special considerations in pregnancy:*** Pregnant women with primary CMV infection can transmit the disease to the fetus, causing congenital infection in infants.

#### **4.4. Molluscum contagiosum :**

##### ***Clinical manifestations:***

Lesions may occur on the skin of any part of the body, most commonly on the face and genitalia, chest, abdomen, arms, thighs. The lesions are often large and persistent, and more difficult to heal compared to HIV (-) persons. Manifest as clear-liquid pearl-like nodules 2 to 10 mm in diameters.

***Diagnosis:*** is usually by clinical appearance of the lesions.

##### ***Treatment:***

- HAART can prevent the development of molluscum contagiosum and cure the lesions, when they already occur.
- Cryotherapy or curettage is effective and is the treatment of choice. If the patients did not respond to these methods, use topical imiquimod or cidofovir.

#### **4.5. Genital warts**

***Clinical manifestations:*** The prevalence of warts in HIV-infected population is higher; the lesions are more extended and persistent; the disease is more difficult to treat and the risk of cancer is increased compared to HIV free population. The disease usually occurs when the TCD4 count is < 500 cells/mm<sup>3</sup>.

- Warts present as soft, moist, pink cauliflower-like papules. Lesions are umbilicated, painless and easily bleed.
- In men condylomata are found most frequently at the frenum or coronal sulcus, penis and urethral meatus.
- In women, warts often occur at posterior introitus and adjacent labia, around urethral meatus, perineum.
- Cervical intraepithelial neoplasia and anal cancer may be asymptomatic or can cause bleeding.

***Diagnosis:*** Mostly based on physical examination alone; do PCR, if possible. Due to high prevalence of HPV infection in HIV-infected women and associated high risk of neoplasia, PAP smear is recommended every 6 months. Women with atypical lesions in

PAP smear should undergo colposcopy with biopsy and histology for early detection and treatment of cervical cancer.

**Treatment:** The development of warts and the prevalence of dysplasia can be reduced with HAART. The relapse rate after treatment in HIV-infected patients is higher than HIV-negative persons.

- Treatment for genital warts in external genitalia, vagina and anus:
  - Podophyllin 10-25% applied once daily or 2-3 times weekly, or
  - Trichloroacetic acid 30% applied once daily, or
  - Cryotherapy with liquid nitrogen, carbonic laser or electrosurgical removal.
- Treatment of warts in cervix: cryotherapy, carbonic laser or electrosurgical removal. Podophyllin should not be used for cervical warts.
- Treatment of warts in urethral meatus: cryotherapy, electrosurgical removal or topical application of trichloroacetic acid.
- Treatment of anal warts: cryotherapy or surgical removal.
- Treatment of oral and laryngeal warts: cryotherapy and electrotherapy. Topical treatment can be combined with chemotherapy to reduce the recurrences.

*Attention to podophyllin treatment:*

- Apply only to the lesions, prevent the medicine from contact with normal tissues; allow the applied surface to dry.
- Instruct patients to wash the surface after 1-4 hours.
- Change to another methods if patients do not respond after 4-6 weeks.

**Special considerations in pregnancy**

- Pregnant women with genital warts have high risk of bleeding from the lesions.
- Do not give topical podophyllin to pregnant women with cervical warts

#### **4.6. Viral hepatitis B**

**Clinical manifestations:** HIV infection increases the risk of developing chronic HBV infection after HBV exposure. HIV-infected person with chronic HBV usually have higher rate of virus replication and higher risk of morbidity and mortality from hepatitis B.

- Many HBV infected persons are asymptomatic.
- The disease can present with one or multiple acute episodes, which manifests with malaise, anorexia, right upper quadrant discomfort, jaundice, hepatomegaly, etc. Some patients can develop acute hepatic failure and die.
- Cirrhosis: wasting, ascites, collateral vascularization; liver may be enlarged or decreased in size, hard on palpation; splenomegaly; esophageal varices; coagulation disturbances.
- Liver cancer: malaise, weight loss, jaundice, ascites, fever, etc. The tumors in the liver may be found on physical examination or detected by imaging methods.

**Laboratory diagnosis:**

- HIV-infected persons should have the blood tested for HBsAg. Repeat the test after 6 months to detect chronic infection with HBV.
- HIV/HBV co-infected persons, especially who have symptoms of hepatitis, should have analyses for HBeAg  $\pm$  HBV-DNA, anti-HBe to assess the activeness of the virus and the immune response of the macroorganism to the infection.

- Do AST, ALT, bilirubin, prothrombin time, serum albumin if patients present with symptoms of hepatitis.
- Liver ultrasonography when patients have symptoms or every 6-12 months.
- $\alpha$ -fetoprotein when findings in liver ultrasonography suggestive of hepatocellular carcinoma.
- Liver biopsy when indicated

**Treatment:**

All HIV/HBV co-infected patients should be advised to avoid or limit alcohol consumption. Attention should be given in prescribing hepatotoxic drugs.

- Supporting treatment: in acute episodes of hepatitis, cirrhosis and other end-stage liver diseases are the same as in HIV-uninfected patients.
- Indications for anti-HBV treatment: Consider treatment in following situations:
  - + Active replication of HBV, manifested by positive HBeAg or HBV-DNA  $> 10^5$  copies /ml, or
  - + Elevated ALT  $> 2$  times, or
  - + Histological evidence of active hepatitis and/or cirrhosis on liver biopsy.
- Patients not eligible for anti-HBV treatment should be monitored to detect acute hepatitis
- Special considerations:
  - + If treatment is indicated for both HIV and HBV, the antiviral regimens should include agents, which are active against both HIV and HBV, e.g. lamivudine, tenofovir. Interferon alpha 2a and 2b is not used frequently due to its inferior efficacy compared to oral antivirals, higher frequency of adverse reactions and higher cost.
  - + If patient uses lamivudine monotherapy for hepatitis B, HIV quickly develops resistance to the agent. Avoid this if possible. Use of lamivudine monotherapy for hepatitis B should be taken into consideration when making the choice of ARV therapy later on.
  - + The treatment is considered effective when HBeAg becomes negative, anti-HBe positive, HBV-DNA and liver enzymes decrease. Continue the treatment for at least 1 year or 6 months after seroreversion. Discontinuation of antiviral treatment results in relapse of the disease in some patients. Consider longterm treatment in this patients' group.
  - + Patients not responding to lamivudine (HBeAg, HBV-DNA persist after 12 months of treatment) may have resistant HBV strains. Consider substituting lamivudine with tenofovir or adefovir, if possible.

***Special considerations in pregnancy***

- Pregnant women with acute hepatitis B have the risk of early labor and pre-term delivery. The treatment for hepatitis B during pregnancy is mainly symptomatic.
- Treatment for chronic hepatitis B during pregnancy is not recommended.
- Infants born to HBV-infected mothers should have early HBV vaccination. The first dose of HBV vaccine should be administered within 12 hours after birth, combined with HB human immunoglobulin, if available.

**4.7. Viral hepatitis C**

**Clinical manifestations:** Hepatitis C virus (HCV) co-infection is seen with high frequency in HIV-infected injection drug use patients.

- HCV/HIV co-infected patients usually have the liver disease develops more quickly than HIV-uninfected persons; the risk of hepatotoxicity due to antiretroviral agents is also higher.
- HCV infections rarely are symptomatic in acute period. Most patients progress to chronic hepatitis without any symptoms or with only mild symptoms. Persistent chronic viral hepatitis C can progress to cirrhosis and hepatocellular carcinoma.

**Laboratory diagnosis:**

- HIV-infected persons with history of injecting drug use should be tested for anti-HCV and HCV- RNA, if possible.
- Other analyses (LFT, ultrasonography and histological investigation) are the same as for patients with hepatitis B.

**Treatment:**

- HIV/HCV co-infected patients should avoid consuming alcohol and be careful in using hepatotoxic agents.
- Indications for treatment: consider treatment for cases of chronic hepatitis with risk of progression to cirrhosis, specifically:
  - + Persistent elevation of ALT > 2 times;
  - + High serum HCV-RNA titer;
  - + Liver biopsy shows portal or bridging fibrosis, moderate or severe inflammation.
- Uncompensated cirrhosis patients are contra-indicated for interferon treatment. Mild hepatitis C patients who do not have indications for treatment should be monitored for ALT and liver histology, if possible.
- Treatment regimens:
  - + *Combination regimen:* Interferon(INF) alpha-2a or INF alpha-2b, 3-5 million units (MU), subcutaneous injection, 3 times weekly, or Pegylated INF (Peg-INF) alpha-2a 180 mcg, subcutaneous injection, once weekly, or Pegylated INF alpha-2b 1,5 mcg/kg, subcutaneous injection, once weekly + Ribavirin, po, 600-1200mg (dose by weight), or
  - + Monotherapy with INF alpha-2a, or INF alpha-2b, or pegylated INF.
- Duration of treatment: 24-48 weeks, depending on HCV genotype and virologic response. Best results are achieved when patients have TCD4 count > 500 cells/mm<sup>3</sup>, the HCV strain is other than genotype 1 and the regimen is combination of INF and ribavirin. The treatment should not be continued if the patient does not respond after 12 weeks of therapy (HCV-RNA titer does not decrease below 2 log<sub>10</sub>). Monitor the adverse drug effects and interactions.
- *Supporting and other Treatment:* same as for hepatitis B patients.

**Special considerations in pregnancy**

- The risk of HCV transmission to the infants in pregnant women with HIV/HCV co-infection is higher compared with HIV-seronegative women. The risk of HIV transmission is also higher compared to HCV-seronegative women.
- Treatment for hepatitis C is not recommended during pregnancy.

**4.8. Lymphocytic Interstitial Pneumonitis (LIP)**

**Clinical manifestations:** The disease is commonly seen in older HIV-infected children, rarely causes death, but can lead to chronic respiratory distress.

- The onset is insidious. The child usually manifests with:
  - + Dry cough, dyspnea, clubbing, parotitis, lymphadenopathy.
  - + Hypoxemia, especially when the child is suffering from concurrent respiratory infections.
  - + Chest X-ray: diffuse reticulo-nodular infiltrations, bronchiectasies.

**Treatment:**

- Temporary improvement may be seen with the use of prednisone 1-2mg/kg/day (if PaO<sub>2</sub> < 85-90 mm Hg). Taper dose after clinical response.
- Symptoms are likely to recur after cessation of corticosteroids unless ARVs are initiated.

## **VI. ANTIRETROVIRAL THERAPY**

### **1. GOALS AND PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)**

#### **1.1. Goals of ART**

- Maximal and durable suppression of virus replication
- Restoration of immunologic function
- Reduction of HIV-related morbidity and mortality
- Improve health and prolong life
- Reduce and prevent HIV transmission after exposure

#### **1.2. Principles of ART**

- ART is part of the generally comprehensive measures of medical, psychological, and social care for HIV-infected people.
- Any treatment regimen must contain at least three ARVs (HAART- Highly active anti-retroviral therapy).
- Adherence is essential and determinant to the success of ART.
- ARVs can only inhibit HIV replication and can not cure HIV infection. Therefore, ART is lifelong and HIV-infected people have to apply measures to prevent transmission to other people.
- Patients on ART must have their OI prophylaxis continued until the immune status is recovered.

### **2. When to start ART**

HIV-infected adults or adolescents are eligible for ART when they become AIDS according to their clinical manifestations and/or TCD4 or TLC criteria as follow:

***If TCD4 testing available:***

- Clinical stage IV, irrespective of TCD4 cell count
- Clinical stage III when the TCD4 count < 350 cells/mm<sup>3</sup>
- Clinical stage I, or II with TCD4 cell counts ≤ 200/mm<sup>3</sup>.

***If TCD4 testing unavailable:***

- Clinical stage IV, irrespective of TLC
- Clinical stage II, or III with TLC ≤ 1200/mm<sup>3</sup>

HIV-infected people not eligible for ART must be monitored clinically and immunologically every 3-6 months for disease progress and indications for ART in future.

### **3. First-line ARV regimens**

#### **3.1. Prioritized regimen: d4T + 3TC + NVP**

- Indication: Use as initial ART regimen for most patients
- Dosage and usage:
  - + d4T: 30mg P.O., b.i.d if the patient is less than 60kg, and 40 mg PO, b.i.d if the patient is more than 60kg. Take the dose once in every 12 hours
  - + 3TC: 150mg P.O., b.i.d, once in every 12 hours
  - + NVP: 200mg P.O., once daily for 2 weeks, then 200mg, b.i.d, once in every 12 hours.
- Attention:
  - + Do not use for patients with AST/ALT > 2.5 upper normal limit.
  - + Care should be exercised when the patients on TB drugs with rifamycin. Substitute NVP with other drug (EFV), if possible

#### **3.2. Replacing regimens**

##### **a. d4T + 3TC + EFV**

- Indication: This regimen is given to patients, who can not use NVP (allergy or liver toxicity due to NVP)
- Dosage and usage:
  - + d4T: 30mg PO, b.i.d. if less than 60kg, and 40 mg PO, b.i.d. if more than 60kg. Take the dose once in every 12 hours.
  - + 3TC: 150mg PO, b.i.d, once in every 12 hours.
  - + EFV: 600mg PO, once daily at night
- Attention:
  - + Can be used for patients with hepatitis.
  - + Do not use for pregnant women because of the potential to cause teratogenesis. If used for women in child-bearing age, ensure effective contraception.
  - + Do not use efavirenz with fatty meals because of the potential increase of neurological side effects.
  - + Give efavirenz at night to avoid sleep disturbance.
  - + Do not give to patients with mental problems (currently or in the past).

##### **b. ZDV + 3TC + NVP**

- Indication: This regimen is given to patients, who can not use d4T (allergy, neurological toxicity, pancreatitis, etc.)
- Dosage and usage:
  - + ZDV: 300mg PO, b.i.d, once in every 12 hours.
  - + 3TC: 150mg P.O., b.i.d, once in every 12 hours.
  - + NVP: 200mg P.O., once daily for 2 weeks, then 200mg, b.i.d, once in every 12 hours.
- Attention:

- + Measure hemoglobin before treatment. Do not use this regimen for patients with hemoglobin < 70g/L. Monitor Hgb every 6 months or when patients present with anemia
- + Do not use for patients with ALT (SGPT) > 2.5 upper normal limit.
- + Be cautious when used for patients on TB drugs with rifamycin. Replace NVP with another drug (e.g. EFV), if possible.

**c. ZDV + 3TC + EFV**

- Indication: This regimen is given to patients, who can not use NVP and d4T
- Dosage and usage:
  - + ZDV: 300mg PO, b.i.d, once in every 12 hours.
  - + 3TC: 150mg PO, b.i.d, once in every 12 hours.
  - + EFV: 600mg P.O., once daily at night
- Attention:
  - + Measure hemoglobin before treatment. Do not use this regimen for patients with hemoglobin < 70g/L. Monitor Hgb every 6 months or when patients present with anemia
  - + Do not use for pregnant women because of the potential to cause teratogenesis. If used for women in child-bearing age, ensure effective contraception.
  - + Give efavirenz at night to avoid sleep disturbance.
  - + Do not use efavirenz with fatty meals because of the potential to increase neurological side effects.
  - + Do not give to patients with mental problems (currently or in the past).

**3. Adherence to ART**

Adherence to ART is taking all the prescribed drugs at the right time. Adherence to treatment is essential for ensuring the treatment success and reducing the drug resistance. To ensure the adherence, the following measures should be applied:

**a. Pre-ART counseling:** Patients must be counselled on:

- Benefits of ART.
- Life-long duration of ART.
- Need to apply measures to prevent transmission to other people while on ART and need of OI prophylaxis if indicated
- Need of regular visits to assess the effectiveness of treatment.
- Side effects, monitoring and management
- Potential drug interactions
- Need to adhere to treatment: take prescribed dosages on scheduled dosing time.
  - + Drugs on twice a day dosing should be taken once in every 12 hours.
  - + Missing the dose > 3 times/month can lead to treatment failure.
  - + Sharing the prescribed drugs with other is not allowed.

**b. Organizational and technical measures:**

- Develop an easy-to-follow schedule for pill-taking.
- Provide supporting services with low price or free of charge.

- Respect confidentiality of private information; build up the trust of patients to health care facilities.
- Develop system for monitoring and supporting adherence to treatment.

**c. Family and community supports**

- Identify a family member to support/supervise the treatment; provide counseling and support to supporters/supervisors.
- Encourage HIV patients to participate in adherence supporting activities.
- Mobilize and coordinate social organizations to support adherence to treatment.

**d. Optimizing adherence in IDU:**

- Treat patients in a supportive and non-discrimination environment.
- Promote stability of the lifestyle.
- Identify treatment supporter/supervisor.
- Provide ART in DOT manner, or in intergration with substitution treatment.
- Pay attention to the interaction of ARVs and opiate.
- Encourage patients to have drug rehabilitation treatment.

**Consider ART for patients, who show the readiness to adhere to the treatment:**

- 1. Demonstrating understanding of HIV/AIDS and ART**
- 2. Demonstrating understanding of the importance of adherence**
- 3. Demonstrating understanding of ARV side effects**
- 4. Demonstrating understanding of the need for follow up**
- 5. Availability of treatment supporter/supervisor**
- 6. Life style stability**
- 7. Prior history of treatment adherence for OI, regular visits or participation in pretreatment training courses.**

**5. Clinical and Laboratory Assessment before the initiation of ART**

- Assess patients status, HIV clinical staging
- If patients have TB, OIs and other diseases, refer to section 9.1 and 9.2, Part VI
- If patients are pregnant, refer to section 11 Part VI and section 1 Part VII
- Repeat laboratory analyses as in Table 4 for selecting appropriate regimen and for baseline of monitoring

**6. ART monitoring**

The following schedule of follow-up visits should be applied to patients on ART:

- Every 1-2 weeks in the first month to monitor side effects and strengthen the adherence
- At the 8-12th week after initiating ART
- Then, every 3-6 months.
- Health care workers and collaborators pay frequent home visits, if possible, for patients on DOT and patients, who need support, to strengthen adherence

**6.1. Adherence monitoring**

Patients on ARVs must be monitored to ensure adherence. The causes of adherence failure need to be identified in order to support the patients.

*Reviewing therapy with patient and treatment supporter/supervisor*

- Check the prescribed drugs and their usage.
- Ask about the time and ways the patient actually takes the drugs, number of times the patients missed taking the drugs.
- Count the number of pills left.

If the patient's adherence is poor, find out the causes, whether it is:

- Side effects or newly emerging conditions?
- Forgetting the dose or lack of understanding the indications?
- Running out of the drugs or financial incapability?
- Psychological problems such as denying HIV infection, or not wanting to let others know that they are treated for HIV, or being scared of discrimination?
- Changes in life?
- Lack of support (from family, friends, health care workers)

The patient should be counseled carefully. The patient's problems should be solved to ensure the adherence.

### **6.2. Clinical monitoring**

At each visit, the patients on ART should be assessed clinically for the followings:

- General status, weight, temperature
- Symptoms of side effects or toxicity
- Clinical staging
- Progression of HIV-related symptoms
- Progression of existing OIs, signs of new or recurrent OIs
- Detection of immune reconstitution syndrome (see section 7)
- Potential pregnancy

The followings are signs of response to ART:

- The patient feels better, has more energy for daily activities
- General status improves; gains weight
- Alleviation of HIV-related symptoms
- Alleviation of pre-existing OIs; reduction of OI frequency and severity

### **6.3. Laboratory monitoring**

Patients on ART should have laboratory analyses monitored to identify side effects and assess response to treatment:

- CBC including WBC every 6 months or when patients on ZDV regimen present with anemia
- Liver enzymes AST/ALT – at 1 month after start of NVP, then every 6 months or when patients present with symptoms of hepatitis.
- TCD4 6-12 months, if available
- Pregnancy test if the patients on EFV and can be pregnant

**Table 4: Laboratory monitoring for first-line ARV regimens**

<b>ARV regimen</b>	<b>Pre-therapy assessment</b>	<b>On-therapy monitoring</b>
	CBC, ALT (SGPT)	ALT (SGPT) if symptoms of hepatitis

d4T/3TC/NVP	TCD4, if available	TCD4 q6-12 months, if available, for efficacy
ZDV/3TC/NVP	CBC, ALT (SGPT) TCD4, if available	CBC (or at least Hgb), and ALT (SGPT) if symptoms of anemia or hepatitis TCD4 q6-12 months, if available, for efficacy
d4T/3TC/EFV	Pregnancy test CBC, AST/ALT TCD4, if available	Necessary testing if symptoms of drug toxicity TCD4 q6-12 months, if available, for efficacy
ZDV/3TC/EFV	Pregnancy test CBC, AST/ALT TCD4, if available	CBC (or at least Hgb) if symptoms of anemia TCD4 q6-12 months, if available, for efficacy

#### d. Side effects monitoring

- Patients on ART should be counselled on the side effects of the drugs and required to report the side effects to doctors when these occur.
- Most of the side effects are mild and occur primarily in the first two weeks of specific treatment, requiring only supportive treatment and disappear within 1 to 2 months (Table 5: Mild adverse reactions of first line regimen and management). However, there might be serious side effects requiring change of regimen (Table 6: Major toxicity of ARVs and management).
- The side effects of ARV should be monitored clinically and with laboratory testing, if indicated and feasible.

**Table 5: Mild adverse reactions of first line regimens and management**

Mild adverse reactions	Common treatment
Nausea	Take with foods
Diarrhea	Water and electrolyte replacement. Antidiarrheals such as loperamide can give temporary relief.
Headache	Paracetamol; if continues for 2 weeks, need follow-up visit
Fatigue	Usually lasts for 4-6 weeks, if persists, need follow-up visit
Abdominal discomfort	If continuous, need follow-up visit
Mild rash	Treat with anti-histamine or steroids. If severe, consider drug allergy
Somnolence	Take drugs before bedtime
Insomnia	Can use supportive drugs
Night mare, dizziness	Take EFV at bedtime; usually does not last > 3 weeks

**Table 6: Major toxicity of ARVs and management**

<b>Toxicity</b>	<b>Related Drugs</b>	<b>Characteristics</b>	<b>Management</b>
Peripheral neuropathy	d4T, ddI, other NRTIs	<ul style="list-style-type: none"> <li>- Usually occurs within first year.</li> <li>- Manifestations: peripheral sensory disturbances, mostly in distal limbs, like wearing gloves; difficulties in walking due to pain.</li> </ul>	<ul style="list-style-type: none"> <li>- Treat with amitriptyline 25mg once a day or group B vitamins.</li> <li>- <i>If severe</i> – substitute d4T or ddI with AZT.</li> </ul>
Pancreatitis	d4T, ddI	<ul style="list-style-type: none"> <li>- Abdominal pain, nausea, vomiting, fever, etc.</li> <li>- Increased amylasemia.</li> </ul>	<ul style="list-style-type: none"> <li>- Discontinue all ARVs</li> <li>- When the symptoms resolve - restart with AZT</li> </ul>
Redistribution of fat	NRTIs (d4T), PIs	<ul style="list-style-type: none"> <li>- Fat accumulates on the chest, abdomen, and back; atrophy of fat on arms, feets, buttocks, and cheeks.</li> <li>- Usually persists for lifelong.</li> </ul>	<ul style="list-style-type: none"> <li>- Counsel the patients on body's changes related to ARVs.</li> </ul>
Liver toxicity	NVP, EFV, ZDV, PIs	<ul style="list-style-type: none"> <li>- High risk: persons with chronic liver diseases.</li> <li>- Usually occurs within first 3 months after initiation of treatment.</li> <li>- Increase of liver enzymes of <math>\geq 3</math> times upper normal limits with/without clinical manifestations.</li> </ul>	<ul style="list-style-type: none"> <li>- Discontinue all ARVs if the liver enzymes increased <math>\geq 5</math> times upper normal limits</li> <li>- Restart ARVs when the liver enzymes return to normal. Discontinue NVP forever. Substitute ARVs causing liver toxicity with other drugs.</li> </ul>
Rash	NVP, EFV, ABC	<ul style="list-style-type: none"> <li>- Usually occurs early, within first 1-3 months.</li> <li>- Manifestations can be mild or severe, life-threatening.</li> <li>- Re-challenging with ABC can result in anaphylactic shock.</li> </ul>	<ul style="list-style-type: none"> <li>- Discontinue all ARVs; give supportive treatment until all the symptoms resolve.</li> <li>- Discontinue ABC forever in case of rash. Discontinue NVP, EFV for cases of rash with systemic symptoms.</li> </ul>
Lactic acidosis and fatty liver atrophy	NRTIs (d4T, ddI; rarely – ZDV, 3TC, ABC)	<ul style="list-style-type: none"> <li>- Usually late complications (after several months).</li> <li>- Manifestations: severe fatigue, nausea, vomiting, weight loss, myalgia, hepatomegaly; increased lactic acid, liver enzymes, amylase.</li> <li>- Routine monitoring of lactate levels in persons without symptoms is not helpful.</li> </ul>	<ul style="list-style-type: none"> <li>- Discontinue all ARVs: the symptoms may persist or even worsen after discontinuation of the drugs.</li> <li>- Supportive treatment with oxygen, intravenous fluid and electrolyte supplementation, correction of acidosis.</li> </ul>
CNS toxicity	EFV	<ul style="list-style-type: none"> <li>- Usually occurs early.</li> <li>- Manifestations: severe confusion,</li> </ul>	<ul style="list-style-type: none"> <li>- Consult with Mental Health specialist.</li> </ul>

		mental disturbances, depression	- If severe, stop EFV and substitute with NVP.
Bone marrow toxicity	ZDV	- Usually occurs within 1 year after initiation of treatment. - Manifestations: severe anemia, may come along with low white blood cells	- Stop ZDV, replace with another NRTI.
Muscle toxicity	NRTIs: d4T, ddI, ZDV	- Usually late complication - Manifestations: myalgia, increased creatinine kinase	- If manifestations are mild – treat with analgesics - If severe – replace the drugs that cause muscle toxicity with 3TC or ABC.
Hyperglycemia and dislipidemia	PIs, EFV	- Usually late complication - Manifestations: increased blood glucose and cholesterol	- Supportive treatment with insulin, low fat diet, continue the ARVs. - If not effective and manifestations are severe – substitute the offending drugs with others.
Kidney calculi	IDV	- Occurs at any stage of treatment, seen more in children. - Manifestations of kidney calculi	- Advise patients to drink more fluids and continue IDV. - If patients can not drink a lot of fluids, consider replacing IDV with another ARV.

## 7. Immune Reconstitution Syndrome

After the start of ART, the immune function of HIV-infected patients begins to recover, causing inflammatory response to opportunistic infections or auto-immune diseases. Certain OIs with no clinical manifestations before the treatment may reactivate or may present with atypical signs and symptoms. The occurrence of illnesses related to immune reconstitution is defined as immune reconstitution syndrome.

Immune reconstitution syndrome usually occurs within 2-12 weeks after the start of ART and seen more frequently in patients with severe immunodeficiency (TCD4 < 50 cells/mm<sup>3</sup>). In rare cases, the immune reconstitution syndrome occurs later, many months after initiation of ART.

The immune reconstitution syndrome is frequently related to TB, other OI, e.g. MAC, PCP, cryptococcal meningitis, other fungal infections, hepatitis B and C, CMV, HSV and HZV, progressive multifocal leucoencephalopathy, toxoplasma encephalitis, etc. Some non-infectious illnesses that can worsen with immune reconstitution syndrome are psoriasis, goiter.

**Clinical manifestations:** The patient can present with fever, lymphadenopathy, and other manifestations, depending on the OIs involved.

### Management:

- + Look for the related OIs, give appropriate treatment.

- + Continue the ARVs; change the components and the dosage of ARVs if interaction or increased toxicity occurs when used concurrently with OI drugs.
- + If manifestations of immune reconstitution syndrome are severe, discontinue the ART. Treat OIs, then restart ART with the same regimen
- + Give symptomatic treatment with non-steroidal anti-inflammatory drugs. If manifestations are severe, prednisolone or methylprednisolone can be given with the dose of 1mg/kg/day with tapering after after 1-2 weeks

#### 4. Treatment failure and second-line regimens

Patients on ARVs must be monitored clinically and immunologically for treatment failure. Treatment failure is considered when the patients have properly adhered to the therapy but still have the following course of clinical manifestations and laboratory analyses:

**Table 7: Signs of treatment failure in adults and adolescents**

Clinical criteria	TCD4 Cell Criteria
<ul style="list-style-type: none"> <li>- The patients on ART but do not gain weight; occurrence of new OIs or malignancy signifying clinical disease progression.</li> <li>- Recurrence of prior OIs</li> <li>- Occurrence or recurrence of clinical stage III conditions</li> </ul>	<ul style="list-style-type: none"> <li>- Return of TCD4 cell count to pre-therapy baseline or below without other concomitant infection to explain transient TCD4 cell decrease</li> <li>- &gt;50% fall from on therapy TCD4 peak level without concomitant infection to explain transient TCD4 decrease.</li> </ul>

**Second-line ARVs:** given when the patients are defined as cases of treatment failure to first line regimens.

**TDF or ABC + ddI + LPV/r or SQV/r or NFV**

#### Dosage and usage:

- TDF: 300mg PO, once a day
  - ABC: 300mg PO, b.i.d, once in every 12 hours
  - ddI: <60kg – 125mg PO, b.i.d, once in every 12 hours  
≥60kg – 200mg PO, b.i.d, once in every 12 hours
  - LPV/r: 400mg/100mg PO, b.i.d, once in every 12 hours, take with foods
  - SQV/r: 1000mg/100 mg PO, b.i.d, once in every 12 hours, take with foods
  - NFV: 1250mg PO, b.i.d, once in every 12 hours, take with foods
- (Adverse drug reactions: see Annex 7: Characteristics of ARVs)

#### Attention:

- + Do not use single ARV to replace or add to a failing regimen.
- + If the virus is highly resistant to AZT, d4T and 3TC, the potency of other NRTIs in the second-line regimens can be compromised, due to cross resistance between the nucleosides. However, ABC, ddI and TFV can still be used.

- + Because of the cross resistance between EFV and NVP, do not use these two drugs to substitute each other in case of treatment failure. Use PI-containing regimen with ritonavir boosting, such as SQV/r, LPV/r. NVP can be considered as replacement for PI drugs in case no PI/r is available or the regimen is contra-indicated.
- + TDF and ddI can be antagonistics. Avoid this combination if possible. If TDF and ddI combination is to be used, give a ritonavir boosted PI as the third ARV in the regimen and decrease the dose of ddI to 250 mg/day
- + LPV/r and SQV/r require cold chain

**Table 8: Combinations not recommended**

Combination	Reason
Abacavir + tenofovir + lamivudine and Didanosine + tenofovir + lamivudine	Low efficacy
Stavudine + didanosine	Increase peripheral neuropathy, pancreatitis, lactic acidosis
Zidovudine + stavudine	Antagonistic, reduced potency

## 9. ART in patients with Opportunistic Infections and other conditions

### 9.1. ART in patients with TB

**Table 9: ART in TB/HIV patients**

<i>Patient's clinical status</i>	<i>No TCD4 available</i>	<i>TCD4 available</i>
Isolated pulmonary TB, no other conditions of Clinical Stage III or IV	Start and complete TB treatment, then start ART	<b>TCD4 &gt; 350/mm<sup>3</sup></b> Start and complete TB treatment. If no other conditions of Clinical Stage III or IV, withhold ART; consider ART as for other HIV-infected cases. If other Clinical Stage IV conditions present, start ART after the initiation phase of TB treatment. Start earlier if the patient is severely ill.
Pulmonary TB and the patient has other conditions of Clinical Stage III or IV or develops these conditions while on anti-TB treatment	Start TB treatment. Start ART after the initiation phase of TB treatment. Start earlier if the patient is severely ill.	<b>TCD4 between 200-350/mm<sup>3</sup></b> Start TB treatment. Start ART after initiation phase of TB treatment. Start earlier if the patient is severely ill.  <b>TCD4 &lt; 200:</b> Start TB treatment. Start ARV as soon as TB treatment is tolerated (between 2 weeks and 2 months)

Extrapulmonary TB	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)
Patient has active TB while being treated for ARV	Treat TB as recommended by the NTP Continue to ARVs.

### ART regimen for TB patients:

- Use EFV containing regimen for patient on rifamycin:  
**d4T + 3TC + EFV or ZDV + 3TC + EFV**
- If the patient is pregnant or in childbearing age, Efavirenz should be replaced by SQV/r (1000/100mg b.i.d or 1600/200mg, qd) or (LPV/r) (400/400mg, bid) or ABC (300mg b.i.d).
- NVP should only be used if no replacement for EFV as listed above, exists.
- If the patient is on ART and needs to be treated for TB, TB drugs should be given as recommended by the NTP; consider changes of ARVs to avoid drug interactions (e.g. change NVP to EFV)
- Closely monitor the adherence to TB and ARV drugs
- Monitor the drug toxicity, especially when high dose of EFV is given to patients on rifamycin.
- Identify and treat immune reconstitution syndrome. The patients need to be re-evaluated to rule out treatment failure or occurrence of other OIs. If immune reconstitution syndrome is the case, continue both anti-TB drugs and ARVs. If the symptoms are mild, give NSAID should be given. If the patients are severe, give prednisolone or methylprednisolone with the dose of 1mg/kg/day and decrease gradually after 1-2 weeks of treatment.

## 2. ART in patients with OIs and other diseases

HIV patients must be screened for OIs and other diseases before starting ART. Treatment of OIs should be started before ART to avoid drug interactions. Some OIs and HIV related illnesses will be improved when patients are on ART (Table 10: ART in patients with OIs and other conditions).

**Table 10: ART in patients with OIs and other conditions**

OIs and other conditions	Approach
<ul style="list-style-type: none"> <li>- Bacterial pneumonia</li> <li>- Acute infections with fever and patient is seriously ill</li> <li>- Diarrheal illnesses (more than 5 loose stools per day)</li> </ul>	<p>Treat these conditions first Start ART when OI treatment is completed, general status of the patient is stable and ARVs can be tolerated.</p>

<ul style="list-style-type: none"> <li>- Pneumocystis pneumonia (PCP)</li> <li>- Cryptococcal meningitis</li> <li>- Toxoplasmosis</li> <li>- Penicilliosis</li> <li>- Esophageal candidiasis</li> </ul>	<p>Treat these illnesses first. Start ART when initial phase of OI treatment is completed or when the patient can tolerate ARVs easily.</p>
<ul style="list-style-type: none"> <li>- Elevated ALT 3-5 times higher upper normal limits</li> <li>- Hepatitis B and C</li> </ul>	<p>Look for causes and treat if possible. Avoid ddI, d4T and NVP in patients with active hepatitis. ARV regimens containing 3TC and TDF can also treat hepatitis B</p>
<ul style="list-style-type: none"> <li>- Drug allergy</li> </ul>	<p>Do not start ART during an acute allergic reaction</p>
<ul style="list-style-type: none"> <li>- Anemia</li> </ul>	<p>Look for treatable cause. If no cause found, commence ART with non-AZT containing regimen</p>
<ul style="list-style-type: none"> <li>- MAC</li> <li>- CMV</li> <li>- Diarrhea due to Cryptosporidiosis and Microsporidiosis</li> </ul>	<p>Combine ARV treatment with OI treatment. Monitor drug interaction</p>
<ul style="list-style-type: none"> <li>- Skin conditions such as papular pruritic eruptions, seborrheic dermatitis</li> </ul>	<p>Provide ARV treatment</p>

## VI. ART IN CHILDREN

### 10.1. Indications of treatment

Antiretroviral treatment for HIV-infected children is indicated on the basis of clinical staging of the child (see Annex 2: Pediatric clinical staging), the TCD4 percentage or total lymphocyte count, and the availability of virological testing to confirm the HIV status of the child.

**Table 11: Indication of ART for HIV-infected children**

Children < 18 months	Virological testing available	TCD4 count available	<ul style="list-style-type: none"> <li>- Pediatric stage IV (AIDS), irrespective of TCD4 percentage</li> <li>- Pediatric stage I, II or III, and TCD4 percentage &lt; 20%</li> </ul>
		TCD4 count not available	<ul style="list-style-type: none"> <li>- Pediatric stage IV (AIDS)</li> <li>- Consider treatment for all children in pediatric stage III</li> <li>- Consider treatment for children in pediatric stage II if the total lymphocyte count is &lt; 2500/mm<sup>3</sup></li> </ul>
	Virological testing not available *	TCD4 count available	<ul style="list-style-type: none"> <li>- Pediatric stage IV (AIDS), irrespective of TCD4 percentage</li> <li>- Consider treatment for all children in pediatric stage III</li> <li>- Treat children in pediatric stage I or II only if the TCD4 percentage is TCD4 &lt; 20%</li> </ul>
		TCD4 count not available	<ul style="list-style-type: none"> <li>- Treat only if the child is in pediatric stage IV</li> </ul>
Children > 18 months	TCD4 count available		<ul style="list-style-type: none"> <li>- Pediatric stage IV (AIDS), irrespective of TCD4 count</li> <li>- Consider treatment for all children in pediatric stage III</li> <li>- Pediatric stage I or II, and TCD4 percentage is &lt; 15%</li> </ul>
	TCD4 count not available		<ul style="list-style-type: none"> <li>- Pediatric stage IV (AIDS)</li> <li>- Consider treatment for all children in pediatric stage III</li> <li>- Consider treatment for children in pediatric stage II if the total lymphocyte count is &lt; 1500/mm<sup>3</sup></li> </ul>

\* Perform HIV antibody test when the child is  $\geq 18$  months and the breastfeeding has been discontinued for at least 6 weeks.

### 10.2. First line Pediatric Regimens

- **Prioritized regimen:** **d4T + 3TC + NVP**

- **Replacing regimens :** **d4T + 3TC + EFV, or**  
**ZDV + 3TC + NVP, or**  
**ZDV + 3TC + EFV**

(For dosage and ways of administration, see Annex 8: Antiretrovirals for Pediatric Use)

**Attention:**

- Adherence to therapy in children is especially difficult; parents and care-givers must be counselled carefully on adherence.
- Drugs are given on the basis of weight and need to be adjusted as the child grows. (see Annex 7: Antiretrovirals for Pediatric Use)
- Most ARVs used for adults can be given to children. If adult formulation is used for children, be cautious in splitting or cutting the pills (use knives) to avoid overdosing (causing toxicities) or under-dosing (causing drug resistance). (See Annex 8: Antiretrovirals for Pediatric Use)
- Do not use EFV for children under 3 years of age or weighing less than 10kg.
- EFV-containing regimens should be used in children over 3 years of age, who are on TB treatment with rifamycin.
- For HIV-infected children under 3 years of age, who are receiving rifamycin containing TB treatment, use AZT + 3TC + ABC regimen; for dosage and ways of administration, see Annex 8: Antiretrovirals for Pediatric Use.

**10.3. Monitoring the treatment**

**Clinical monitoring:** Children on ARV need to be monitored with weight, OI frequency, etc., as recommended for adults. In addition, special attention should be paid to:

- Nutritional status of the child and feeding practice
- Physical development (height and weight by age)
- Psychological development by age
- Cognitive and social development
- Drug side effects

**Laboratory:** Basic tests as for adults; pay attention to TCD4%

**Table 10: Signs of ART failure in children**

<b>Clinical signs</b>	<b>Laboratory</b>
- The initially responsive child stops gaining weight or loses weight	- TCD4 count or percentage remains at the same level as baseline or lower.
- No improvement in psychological development or occurrence of new encephalopathy conditions	- TCD4 count returns to the prior treatment level or lower without any causes.
- Occurrence of new OIs or tumors, indicating the progression of HIV disease	- TCD4 count (or percentage) decreases more than 50% against the maximum level reached since treatment initiation without any causes.
- Recurrent OIs	

#### **10.4. Second line ARV regimens for Infants and Children**

Indicated when first-line regimens fail.

<b>ABC + ddI + LVP/r or NFV</b>
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(Dosage and ways of administration, see Annex 8: Antiretrovirals for Pediatric Use)

#### **11. ART in Pregnant Women**

- Women who meet treatment criteria as for other adults should have ART started (see criteria for initiation of ART in adults).
- HIV-infected pregnant women, ARV naive: Do not initiate ART in the first 12 weeks of pregnancy to minimize the toxicity of ARVs to the fetus.
- HIV-infected women, who got pregnant while on ARVs: continue ARVs but do not use efavirenz in the first trimester.

##### **Regimens**

- **Prioritized regimen:**                    **ZDV + 3TC + NVP**  
Doses: Similar to adult doses.
  
- **Replacing regimens:**        **ZDV + 3TC + NFV, or**  
   **ZDV + 3TC + SQV/r or LPV/r**

##### **Dosage:**

- Nelfinavir 1250mg PO, b.i.d.
- Saquinavir/ritonavir 1000 mg/100 mg PO, b.i.d.
- Lopinavir/ritonavir: 400mg/100mg, b.i.d

##### **Attentions:**

- Monitor side effects closely.
- Do not use combination of ddI and d4T for pregnant women to avoid lactic acidosis and liver toxicity.
- Do not use combination of ZDV and d4T.

### **VII. PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV AND POST-OCCUPATIONAL EXPOSURE PROPHYLAXIS**

#### **1. Prevention of Mother-to-Child Transmission of HIV**

Pregnant women with HIV, who are not on ARV, should receive PMTCT regimen appropriate for the time they appear for antenatal care and the time their HIV infection is detected. Pregnant women, who are on ART, do not need independent PMTCT. All infants born to HIV-infected mothers should receive prophylaxis with ARV after birth.

#### **1.1. PMTCT Regimens and Indications for Use**

**Table 11: PMTCT Regimens and Indications for Use**

<b>Regimen – Indications</b>	<b>Mothers</b>	<b>Infants</b>
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<b>ZDV + NVP</b> The mothers appear to ANC and are defined as HIV(+) before 28-36 weeks of pregnancy	<b>Antepartum:</b> ZDV 300mg b.i.d from 28 weeks of pregnancy until onset of labor. <b>Intrapartum:</b> ZDV 600mg + NVP 200mg single dose at the onset of labour	<b>Used for all regimens:</b>  NVP sirup 6mg (6ml) if the newborn weighed > 2kg and 2mg/kg if ≤ 2 kg within 48 hours after birth* + ZDV sirup 2mg/kg/every 6 hours from birth x 1 week *****
<b>NVP</b> The mothers appear to ANC/defined as HIV(+)** right before labor	<b>NVP</b> 200mg single dose at the onset of labour*** or 4 hours before cesarian section.	
<b>3-drug regimen</b> The mothers appear to ANC and are defined as HIV(+) after 36 weeks but are not in labor*****.	<b>AZT/d4T + 3TC + NFV/SQV/r</b> Take every day until labor with the dose similar to therapeutic dose.	

\* If the mothers have been on PMTCT regimen for less than 4 weeks, if the mothers have not taken NVP during labour or have taken NVP within 1 hour before delivery, ZDV can be given to infants for up to 4-6 weeks.

\*\* Give PMTCT if at the time of labor/cesarian section the mothers have only one positive serological test for HIV; do confirmatory test thereafter.

\*\*\* Do not give NVP to mothers if it has been taken at false labour or if imminent delivery (within 1 hour) is anticipated.

\*\*\*\* If the mothers have not taken NVP during labour or have taken NVP within 1 hour before delivery, give NVP sirup to newborn right after birth.

\*\*\*\*\* If possible, consider 3-drug PMTCT regimen, starting after 14 weeks and before 28 weeks of pregnancy and continue until delivery.

## 1.2. General Recommendations

### Antepartum:

- Give counselling and support
- Discuss with the mothers about the method of delivery and feeding

### Intrapartum:

- Follow strict measures of aseptics during delivery
- Do not perform early amniotomy; avoid interventions that cause bleeding in birth canal during delivery.
- Do cesarean section only if indicated by obstetric conditions.
- Avoid procedures and interventions that cause disruptions to the skin of the fetus, such as placing electrodes on the head, drawing venous blood from forehead for pH testing.
- Wash the newborn right after birth.

### Postpartum:

- Counsel the mothers about the risk of HIV transmission with breast feeding; encourage full replacement feeding for infants. If full replacement feeding is not possible, counsel the mother to give exclusive breast feeding for the first 4-6 months.
- HIV-infected mothers after the delivery must be monitored and considered for ART like other HIV-infected people.

- Neonates must be followed and tested for HIV status, OI prophylaxis, and consider for ART as indicated in treatment for children.
- Women and children exposed to ARVs as PMTCT regimens can still be treated with these drugs in the following regimens if indicated. Due to the risk of drug resistance after PMTCT treatment, monitor patients closely for early detection of treatment failure.

## **2. Post-Occupational Exposure Prophylaxis**

Occupational exposure to HIV is considered when direct contact with HIV-infected blood or body fluids occurs, what can result in transmission of HIV.

### **2.1. Modes of exposure:**

- Needle stick while performing injection, taking blood sample, fluid tapping, etc.
- Wounds from surgical scalpels, other sharp instruments.
- Percutaneous wounds from broken tubes, which contain patient's blood or body fluids.
- Pre-existing skin lesion (eczema, burn, old ulcer, inflammation) contaminated with patient's blood or body fluids.
- Others: injection by contaminated needles when chasing criminals, etc.

### **2.3. Management after exposure:**

#### **2.2.1: Treatment of exposure site**

- Bleeding wound of the skin:
  - Flush the wound with tap water.
  - Let the wound bleed for a short time.
  - Clean with water and soap, then treat the wound with an antiseptic solution (Dakin, Javel 1/10, or alcohol 70%) for at least 5 minutes.
- Eye exposure: Wash the eyes with distilled water or NaCl 0,9% solution continuously for 5 minutes
- Mouth and nose exposure:
  - Rinse with distilled water or NaCl 0,9% solution.
  - Gargle with NaCl 0,9% solution for several times.

**2.2.2. Report the exposure to the manager and complete the report:** state the time and context of exposure, description of wound, and level of risk.

**2.2.3. Define the HIV status of the source of exposure**

**2.2.4. Define the HIV status of exposed person**

**2.2.5. Assessment of risk**

- High Risk:
  - Deep wounds with large bleeding, caused by large-bore needles.
  - Deep and large percutaneous wounds with bleeding, caused by scalpels or broken blood containing tubes.
  - Large lesions on the skin or mucus membranes (e.g. eye, nose) exposed to patient's blood or body fluids.
- Low Risk
  - Shallow wounds with minor bleeding or no bleeding
  - Intact mucosae exposed to patient's blood or body fluids.
- No Risk: Contact of normal skin with patient's blood or body fluid.

### 2.3. Counseling for the exposed person:

- Risk of infection with HIV, HBV, HCV
- Symptoms suggestive of side effects of ARVs and primary HIV infection: fever, rash, nausea or vomiting, anemia, lymphadenopathy, etc.
- Prevention of HIV transmission to others: Exposed persons may transmit HIV to others even if the test is temporarily negative (the window period), and they, therefore, should practice measures to prevent transmission.

### 3. ARV prophylaxis for exposed persons

#### Indications:

- Exposures with no risk: No treatment
- Exposures with low risk: Give treatment only when the source is HIV-positive and the exposed person is HIV-negative
- Exposures with high risk:
  - + Give ARV treatment right after exposure for exposed persons; test the exposure source. Discontinue the treatment if the source is HIV-negative.
  - + ARV treatment should be given early, 2 - 6 hours after exposure and should not be delayed beyond 72 hours.

#### ARV prophylaxis regimens

	High risk exposure	Low risk exposure
<b>Treatment regimens</b>	ZDV + 3TC <i>or</i> d4T + 3TC <i>plus:</i> NFV/LPV/r <i>or</i> EFV	ZDV + 3TC <i>or</i> d4T + 3TC
<b>Duration of treatment</b>	4 weeks	
<b>Follow-up</b>	<ul style="list-style-type: none"><li>- Do HIV testing after 1, 3 and 6 months.</li><li>- Do laboratory tests to monitor side effects of ARV: CBC, ALT (SGPT) on the start of treatment and after 2 weeks; blood glucose if using NFV or LPV/r</li></ul>	

- Dosage and ways of administration:
  - + ZDV: 300mg PO, b.i.d
  - + 3TC: 150mg PO, b.i.d
  - + d4T: < 60kg - 30mg PO, b.i.d  
≥ 60kg - 40mg PO, b.i.d
  - + NFV: 1250mg PO, b.i.d
  - + LPV/r: 400mg/100mg P.O, b.i.d
  - + EFV: 600mg PO, at bedtime

## **E- ANNEX/SUPPLEMENTATIONS**

### **Annex 1: WHO Staging System for HIV infection in adults**

#### **Clinical Stage 1**

- Asymptomatic
- Persistent generalized adenopathy
- Performance scale 1: asymptomatic, normal activity

#### **Clinical Stage 2**

- Weight loss, <10% body weight
- Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent P.O. ulcerations, angular cheilitis)
- Herpes zoster within last 5 years
- Recurrent upper respiratory infections (e.g. sinusitis)
- And/or performance scale 2: symptomatic, normal activity

#### **Clinical Stage 3**

- Weight loss, >10% body weight
- Unexplained chronic diarrhea, > 1 month
- Unexplained prolonged fever (intermittent or constant), > 1 month
- P.O. candidiasis (thrush)
- P.O. hairy leukoplakia
- Pulmonary tuberculosis with in past year
- Severe bacterial infections (e.g. pneumonia, pyomyositis)
- And/or performance scale 3: bed-ridden <50% of day during last month

#### **Clinical Stage 4**

- HIV wasting syndrome (weight loss of >10%, plus either unexplained chronic diarrhea > 1 month, or chronic weakness and unexplained prolonged fever > 1 month)
- *Pneumocystis jiroveci* pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhea, > 1 month
- Cryptococcosis, extrapulmonary
- Cytomegalovirus disease of an organ other than liver, spleen or lymph nodes
- Herpes simplex virus infection, mucocutaneous > 1 month or visceral
- Progressive multifocal leukoencephalopathy
- Any disseminated endemic mycosis ( e.g. histoplasmosis, penicilliosis)
- Candidiasis of the esophagus, trachea, bronchi or lungs
- Disseminated non-tuberculous mycobacteriosis
- Non-typhoid *Salmonella* bacteremia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV encephalopathy (Clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progression over weeks)

or months, in the absence of a concurrent illness or condition other than HIV infection that could explain findings

- And/or performance scale 4: bed-ridden >50% of the days of the previous month.

## **Annex 2: Pediatric Clinical Staging**

### **Stage I:**

Asymptomatic  
Persistent generalized lymphadenopathy (PGL)  
Hepatosplenomegaly

### **Stage II:**

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, 2 or more episodes in any 6 month period)  
Papular pruritic eruption  
Herpes zoster (1 or more episodes in 6 months)  
Recurrent oral ulcerations (2 or more episodes in 6 months)  
Lineal gingival Erythema (LGE)  
Angular cheilitis  
Parotid enlargement  
Seborrheic dermatitis  
Extensive Human papilloma virus infection (more than 5% body area or disfiguring)  
Fungal nail infection

### **Stage III:**

Unexplained moderate malnutrition\* not adequately responding to standard therapy  
Unexplained persistent diarrhea (more than 14 days)  
Unexplained persistent fever (intermittent or constant, for longer than 1 month)  
Oral candidiasis (outside neonatal period)  
Oral hairy leukoplakia  
Pulmonary TB\*\*  
Severe recurrent presumed bacterial pneumonia (2 or more episodes in 6 months)  
Acute necrotizing ulcerative gingivitis/periodontitis  
Lymphoid interstitial pneumonitis (LIP)  
Unexplained anemia (< 8gm/dL), neutropenia (<1,000/mm<sup>3</sup>) or thrombocytopenia (<30,000/mm<sup>3</sup>) for more than 1 month  
Chronic HIV associated lung disease including bronchoectasis  
HIV related cardiomyopathy or HIV related nephropathy

### **Stage IV:**

*Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:*

Unexplained severe wasting or severe malnutrition\*\*\* not adequately responding to standard therapy

Pneumocystis pneumonia  
 Recurrent severe presumed bacterial infections (2 or more episodes within 1 year, e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)  
 Chronic orolabial or cutaneous Herpes simplex infection (of more than 1 month duration)  
 Extrapulmonary TB  
 Kaposi's sarcoma  
 Esophageal Candida  
 CNS Toxoplasmosis  
 HIV encephalopathy

*Conditions where confirmatory diagnostic testing is necessary:*

CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymphnodes onset at age 1 month or more)  
 Cryptococcal meningitis (or other extrapulmonary disease)  
 Any disseminated endemic mycosis (e.g. extrapulmonary Histoplasmosis, Coccidiomycosis, Penicilliosis)  
 Cryptosporidiosis  
 Isosporiasis  
 Disseminated non-TB mycobacteria infection  
 Candida of trachea, bronchi or lungs  
 Acquired HIV related recto-vesico fistula  
 Cerebral or B cell non-Hodgkin's lymphoma  
 Progressive multifocal leucoencephalopathy (PML)

**Diagnosis of Clinical Stage IV in children less than 18 months old where virological testing is not available**

HIV seropositive children with  $\geq 2$  of the following conditions are considered in clinical stage IV:

- Oral thrush
- Severe pneumonia
- Severe wasting/malnutrition
- Severe sepsis

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\* Defined as very low weight for age

\*\* TB may occur at any CD4 count and CD4% should be considered where available

\*\*\* Defined as very low weight or visible severe wasting or edema of both feet

**Annex 3: Immunologic categories for HIV-infected children Based on age-specific TCD4 lymphocyte counts and percentage of total lymphocytes (Adapted from CDC 1994 revised classification system for human Immunodeficiency virus infection in children less than 13 years of age)**

Immunologic categories	Children ≤12mos TCD4/μl (%)	1 - 5 years TCD4/μl (%)	6 - 12 years TCD4/μl (%)
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I- No suppression	≥ 1,500 (≥25)	≥ 1,000 (≥25)	≥ 500 (≥25)
II- Moderate suppression	750 – 1,499 (15-24)	500 – 999 (15-24)	200 – 499 (15-24)
III- Severe suppression	< 750 (<15%)	< 500 (<15%)	< 200 (<15%)

#### **Annex 4: Advice on Healthy Living for Persons with HIV/AIDS**

##### **Daily activities:**

- Use good hygiene, including frequent hand washing with soap and water.
- Wash hands well after contact with raw meat and with soil after gardening/farming, after going to the toilet and always before eating.
- Avoid cleaning cat feces, bird droppings; avoid contacting human feces. Avoid contact with cats and reptiles.
- Avoid swimming in lakes, rivers, pools, salt water beaches, which may all be contaminated with human or animal waste.

##### **Eating and drinking:**

- Consume water that has been boiled (3 minutes) or is bottled; ice should be prepared from boiled or bottled water.
- Avoid raw or undercooked eggs, poultry, meats, fish, sea foods, and unpasteurized dairy products.
- If raw fruits and vegetables cannot be peeled, clean them thoroughly (e.g., with dilute bleach & clean water solution) before consuming.

##### **Healthy living:**

- Don't smoke, or if you can't stop, cut down.
- If have sex, use a latex condom; use correctly and right from the beginning of sex. Use contraceptives to prevent unwanted pregnancies.
- Avoid people who are coughing (TB, pneumonia) or who have chicken pox or shingles (zona).

#### **Annex 5: Common infections in HIV based on TCD4 count#**

TCD4 > 500 cells/mm <sup>3</sup>	Acute retroviral syndrome Infections common in general population of region. Candida vaginitis Persistent Generalized Lymphadenopathy HIV related aseptic meningitis Salmonella bacteremia Syphilis Septic endocarditis (especially in i.v. drug addicts caused by staphylococcus)
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500-200 cell/mm <sup>3</sup>	Pneumococcal and other bacterial pneumonia Pulmonary tuberculosis Herpes zoster Oropharyngeal candidiasis Cryptosporidiosis (acute episodes) Kaposi's sarcoma* P.O. hairy leukoplakia* Bacillary Angiomatosis ( <i>Bartonella henselae</i> or <i>Bartonella quintana</i> ) Fever due to HIV virus Cervical intraepithelial carcinoma and cervical carcinoma* Lymphocytic interstitial pneumonitis*
< 200/mm <sup>3</sup>	Pneumocystis carinii pneumonia Disseminated histoplasmosis Disseminated coccidiomycosis Miliary/extrapulmonary TB Progressive multifocal leukoencephalopathy* Non Hodgkin's Lymphoma* Nocardiosis Wasting syndrome
<100/mm <sup>3</sup>	Disseminated Herpes Simplex Virus Toxoplasmosis Cryptococcosis Chronic Cryptosporidiosis Microsporidiosis Candida Esophagitis Visceral Leishmaniasis
<50/mm <sup>3</sup>	Disseminated <i>Penicillium marneffeii</i> Disseminated infection with Mycobacterium avium complex and other mycobacterium ( <i>M. kansasii</i> , <i>M. haemophilum</i> , <i>M. goodii</i> , <i>M. fortuitum</i> , etc.) Disseminated Cytomegalovirus Lymphoma of Central Nervous System*

# With every level of Immunodeficiency, certain opportunistic infections can occur **plus** any disease(s) characteristic for the preceding immune stages;

\* These tumors are related to infection of certain viruses, e.g. Epstein-Barr, Herpes 8, JC virus, etc.

#### **Annex 6: Adverse reactions of drugs used for treatment and prophylaxis of opportunistic infections**

<b>Adverse reactions</b>	<b>Drugs</b>
Bone marrow suppression	Cidofovir, dapsone, ganciclovir, pyrimethamine, rifabutin, sulfadiazine, TMP-SMZ
Diarrhea	Atovaquone, clindamycin

Hepatotoxicity	Clarithromycin, fluconazole, isoniazid, itraconazole, ketonazole, pyrazinamide, rifabutin, rifamycin, TMP-SMZ
Nephrotoxicity	Amphotericin B, cidofovir, foscarnet, pentamidine, acyclovir (high dose)
Eyes' effect	Cidofovir, ethambutol, rifabutin
Hepatitis	Pentamidine, TMP-SMZ
Peripheral neuritis	Isoniazid
Neurotoxicity	Acyclovir (high dose), quinolones
Skin eruptions	Atovaquone, dapsone, pyrimethamine, sulfadiazine, TMP-SMZ, ribavirin

**Annex 7: Characteristics of ARV Drugs**

<b>Drug name</b>	<b>Abbreviation</b>	<b>Dosage</b>	<b>Number of pills daily</b>	<b>Affects of food</b>	<b>Side effects</b>
<b>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</b>					
Zidovudine (Retrovir)	AZT ZDV	300 mg, twice daily	2	No regards	Leukopenia, anemia Fatigue, malaise, headache Nausea, vomiting, hepatitis Myopathy Lactic acidosis with hepatic steatosis
Stavudine	d4T	< 60kg: 30 mg, twice daily ≥60kg: 40 mg, twice daily	2	No regards	Peripheral neuropathy Nausea, vomiting, elevated liver enzymes Lactic acidosis with hepatic steatosis
Didanosine	ddI	< 60kg: 125 mg, twice daily ≥60kg: 200 mg, twice daily  Add EC dosing in case it becomes available	2	No regard	Peripheral neuropathy, headache Pancreatitis, nausea, diarrhea, abdominal pain Rash, fever Lactic acidosis with hepatic steatosis
Lamivudine	3TC	150 mg twice daily or 300mg once daily	2	No regard	Minimal toxicity Headache, insomnia Rash Lactic acidosis with hepatic steatosis
Abacavir	ABC	300 mg once daily	2	No regard; alcohol increases ABC levels 41%	Hypersensitivity reaction (fever, rash, nausea, vomiting, abdominal pain -- can be fatal on rechallenge) Lactic acidosis with hepatic steatosis
Tenofovir	TDF	300 mg once daily	1	No regard	Nausea, vomiting, diarrhea
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>					
Efavirenz	EFV	600 mg at bed time	1	Avoid taking after high fat meals	Rash, Stevens-Johnson CNS symptoms, including insomnia, nightmares, hallucinations, mood

					disturbance Elevated liver enzymes Teratogenic. Contraindicated in pregnancy.
Nevirapine	NVP	200 mg once daily in the first 2 weeks, then 200 mg twice daily	2	No regard	Rash, Stevens-Johnson Elevated liver enzymes
<b>Protease Inhibitors (PIs)</b>					
Indinavir	IDV	800 mg every 8 hours IDV/r: 800mg/100mg twice daily	6	Take 1hr before or 2hr after meals; Separate dosing from ddI by 1hour	Nephrolithiasis Nausea, headache, dizziness, elevated indirect bilirubin, dry skin, hair loss Hyperglycemia, fat redistribution and abnormal lipids
Saquinavir	SQV	1200 mg t.i.d	18	Take with food to improve level. Garlic may reduce saquinavir levels by 50%.	GI intolerance, nausea, vomiting, diarrhea, abdominal pain Headache <b>Hepatitis</b> Hyperglycemia, fat redistribution and abnormal lipids
	SQV/r	SQV/r: 1000mg/100 mg b.i.d			
Nelfinavir	NFV	1250 mg twice daily	10	Take with food to improve level.	Diarrhea Hyperglycemia, fat redistribution and abnormal lipids
Lopinavir/r	LPV/r	LOV/r: 400mg/100mg twice daily	6	No regard	GI intolerance, nausea, vomiting, diarrhea Rash Headache <b>Hyperglycemia, fat redistribution and abnormal lipids</b>
Ritonavir	RTV	Mostly used to boost other PIs	12	If use as single PI, take with foods to increase the drug	GI intolerance, nausea, vomiting, diarrhea Altered taste

				concentration and improve the tolerance	<b>Hepatitis</b> Hyperglycemia, fat redistribution and abnormal lipids
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### Annex 8: Antiretrovirals for Pediatric Use

Drug name	Formulation	Dose and using	Other comments
<b><i>I. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</i></b>			
Zidovudine (ZDV)	Syrup 10mg/ml Capsules (can remove cover, use powder with water or food): 100mg; 250 mg Tablet: 300 mg (tablets can be halved, can be crushed )	Age < 4 weeks: 4 mg/kg/ dose b.i.d Age from 4 weeks to 13 years: 180mg/m <sup>2</sup> /dose b.i.d ≥13 years: 180mg/m <sup>2</sup> /dose b.i.d. Maximum dose: 300 mg/dose b.i.d	Do not use with d4T Store in dark glass jars Can be given with food
Lamivudine (3TC)	Syrup 10mg/ml Tablet 150mg	< 1 month: 2mg/kg/dose twice daily > 1 month and < 60kg: 4mg/kg/dose b.i.d Maximum dose: > 60kg: 150 mg b.i.d	Can be given with food Store solution at room temperature, use within one month of opening
Fixed-dose combination of ZDV plus 3TC	No liquid form available Tablet: 300mg ZDV plus 150 mg 3TC	For children > 13 years or > 60 kg: 1 tablet/dose b.i.d	
Stavudine (d4T)	Oral solution 1mg/kg Capsules 15mg, 20mg, 30mg, 40mg	< 30kg: 1mg/kg twice daily 30-60 kgK 30mg twice daily  Maximum dose for ≥ 60kg: 40mg twice daily	Do not use with AZT Keep solution refrigerated; stable for 30 days. Shake well before use. Store in glass bottles. Capsules can be opened and mixed with small amount of foods and water.
Fixed-dose combination of d4T plus 3TC	No liquid form available Tablet: d4T 30mg plus 3TC 150 mg Tablet: d4T 40mg plus 3TC 150 mg	Maximum dose for children: 30-60 kg: one 30-mg-d4T-based tablet b.i.d > 60kg: one 40-mg-d4T-based tablet b.i.d	Tablet should not be split
Didanosine (ddI)	Oral suspension pediatric powder / water 10mg/ml. Chewable tablets 25mg, 50mg,	2 weeks - 3 months: 50mg/m <sup>2</sup> /dose twice daily 3 months - 13 years: 90-120mg/m <sup>2</sup> /dose	Keep suspension refrigerated; stable for 30 days. Shake well before use. Take on empty stomach (30 minutes

	100mg, 150mg, and 200mg Enteric-coated beadlets in capsules: 125mg, 200mg, 250mg, 400mg	b.i.d Maximum dose: > 60kg: 200mg/dose b.i.d	before or 2 hours after eating) Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food
Abacavir	ABC	< 16 years or < 37.5kg: 8mg/kg/dose b.i.d >16 years or > 37.5kg: 300mg/dose b.i.d	Tablet can be crushed and contents mixed with small amount of water or food and immediately ingested. Parents must be warned about hypersensitivity reaction. ABC should be stopped permanently if hypersensitivity reaction occurs.
Fixed-dose combination of ZDV plus 3TC plus ABC	Tablet: ZDV 300mg plus 3TC 150mg plus ABC 300mg	>40mg: 1 tablet/dose b.i.d	
<b>2.Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>			
Nevirapine (NVP)	Syrup 10mg/ml Tablet 200mg (tablets can be halved, can be crushed )	- 15 - 30 days: 5mg/kg/dose once daily x 2 weeks, then: 120mg/m <sup>2</sup> /dose b.i.d x 2 weeks, then: 200mg/m <sup>2</sup> /dose b.i.d x 2 weeks - > 30 days - 13 years: 120mg/m <sup>2</sup> /dose once daily x 2 weeks, then: 120-200mg/m <sup>2</sup> /dose twice daily - Maximum dose: 200mg/dose once daily x 2 weeks, then 200mg/dose twice daily	Avoid to coadministrate with rifampicin. Store suspension at room temperature. Must be well shaken before taking.  Parents must be warned about rash.
Efavirenz (EFZ)	Syrup 30mg/ml Capsules (can be halved to smaller doses) 50mg, 100mg and 200mg	- Maximum dose: 600mg once daily > 3 years: capsules or suspension 10 - 15kg : 200mg (270mg = 9ml) once daily 15 - 20kg : 250mg (300mg = 10ml) once daily 20 - 25kg : 300mg (360mg = 12ml) once daily 25 - 33kg : 350mg (450mg = 15ml) once daily 33 - 40kg : 400mg (510mg = 17ml) once	Dizziness, nightmares.  Only for children over 3 years of age  Best to use at night

		daily	
<b>3. Protease Inhibitors (PIs)</b>			
Nelfinavir (NFV)	Powder for oral suspension mix with liquid 200mg/5ml (50mg per 1,25ml) Tablet 250mg - (tablets can be halved, can be crushed and added to food or dissolved in water)	- < 1 year : 50mg/kg/dose t.i.d or 75mg/kg/dose b.i.d - >1-13 years : 55 - 60mg/kg/dose b.i.d	Higher doses in infants < 1 years. Do not use acidic food. Preferred to use of crushed tablets. Take with food.
Lopinavir/Ritonavir (LPV/r)	Syrup: 80mg/ml Lopinavir plus 20mg/ml Ritonavir  Capsules: 133,3mg Lopinavir plus 33,3mg Ritonavir (should not be crushed or opened)	- 6 th,ng - 13 tuæi : 225mg/m2 LPV/ 57,5mg/m2 Ritonavir twice daily or weight-based dosing - 7 - 15kg: 12mg/kg LPV/3mg/kg Ritonavir/dose b.i.d - 15 - 40 kg: 10mg/kg Lopinavir /5mg/kg Rinoavir b.i.d - Maximum dose: > 40kg : 400mgLPV/100mg Ritonavir (3 capsules or 5ml) b.i.d	Oral solution and capsules should be refrigerated, can be stored at temperature below 25oC for 2 months. In temperature above 25oC, the drug degrades more rapidly.  Take with food.  Interact with many drugs.

### Annex 9: Interactions of ARVs

Antiretrovirals	Interacted Drugs	Mechanism/effect	Recommendations
LPV/r	Clarithromycin	Decreased metabolism, clarithromycin concentration increased	Adjust clarithromycin dose only in renal failure.
EFV, NVP	Clarithromycin	Increased metabolism, clarithromycin concentration decreased	The efficacy of MAC treatment and prophylaxis may be decreased; closed monitoring is needed.
EFV	Rifabutin	Increased metabolism, significant decrease in rifabutin levels/ Efavirenz level may decrease	Increase rifabutin dose to 450-600mg daily or 600mg twice weekly.

			No dosage change necessary for efavirenz.
ddI	Gancyclovir	ddI level increased up to 100%	Monitor for ddI-related adverse reactions.
LPV/r	Ketoconazole	Decreased metabolism, ketoconazole concentration increased	Use with caution at ketoconazole doses > 200 mg/day
ddI	Fluoroquinolone antibiotics	Mark decrease in quinolone drug levels because of cationization	Administer didanosine at least 2 hours after quinolone.
DLV	Rifabutin	Increased metabolism, significant decrease in delavirdine levels	Avoid concurrent use of these 2 drugs.
RTV, LPV/r, SQV/r, IDV, NFV, APV	Rifabutin	Decreased metabolism, significant increase in rifabutin levels/ Increased metabolism, saquinavir	Decrease rifabutin to 150mg every other day or 3 time per week. No dosage change for PIs.
NVP, APV, DLV, IDV, LPV/r, NFV, SQV	Rifamycin	Increased metabolism, mark decrease in PI or delavirdine levels	Avoid concurrent use.
EFV, RTV, SQV/r, NVP	Rifamycin	Increased metabolism, decrease in PI or nevirapine levels	Possible combination use. Consider increase in efavirenz dose to 800mg a day when used with rifamycin.
d4T, NVP, EFV, RTV, SQV, NFV, LPV	Methadone	Decreased methadone concentration	Abstinence syndrome can occur; may require increase in methadone dose
IDV, ATV	Contraceptives Norethindrone, Ethinyl estradiol	Increased concentration of contraceptives	No need to adjust doses of contraceptives
NVP, RTV, NFV, APV, LPV	Ethyl estradiol	Mark decrease in Ethyl estradiol concentration	Use alternative or supportive contraception methods.
ddI	TDF	Increased ddI levels	Decrease ddI dose to 250mg a day
IDV, SQV and some other ARVs	Carbamazepine Phenobarbitol, Phenytoin	Decreased levels of IDV, SQV and other ARVs	Caution when use concurrently; consider alternative ARV; monitor adverse reactions of anticonvulsants.

